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(54) Title: AMIDE SUBSTITUTED IMIDAZOPYRIDINES, IMIDAZOQUINOLINES, AND IMIDAZONAPHTHYRIDINES

(57) Abstract: Imidazopyridine, imidazoquinoline, and imidazonaphthyridine compounds having an amide substituent at the 1-position, pharmaceutical compositions containing the compounds, intermediates, and methods of making and methods of use of these compounds as immunomodulators, for modulating cytokine biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases are disclosed.

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AMIDE SUBSTITUTED IMIDAZOPYRIDINES, IMIDAZOQUINOLINES, AND IMIDAZONAPHTHYRIDINES

RELATED APPLICATIONS

The present invention claims priority to U.S. Provisional Application Serial No. 60/555753, filed March 24, 2004, and U.S. Provisional Application Serial No. 60/578769, filed June 10, 2004, both of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

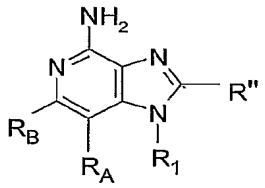
In the 1950's the 1*H*-imidazo[4,5-*c*]quinoline ring system was developed, and 1-(6-methoxy-8-quinolinyl)-2-methyl-1*H*-imidazo[4,5-*c*]quinoline was synthesized for possible use as an antimalarial agent. Subsequently, syntheses of various substituted 1*H*-imidazo[4,5-*c*]quinolines were reported. For example, 1-[2-(4-piperidyl)ethyl]-1*H*-imidazo[4,5-*c*]quinoline was synthesized as a possible anticonvulsant and cardiovascular agent. Also, several 2-oxoimidazo[4,5-*c*]quinolines have been reported.

Certain 1*H*-imidazo[4,5-*c*]quinolin-4-amines and 1- and 2-substituted derivatives thereof were later found to be useful as antiviral agents, bronchodilators and immunomodulators. Subsequently, certain substituted 1*H*-imidazo[4,5-*c*]pyridin-4-amine, quinolin-4-amine, tetrahydroquinolin-4-amine, naphthyridin-4-amine, and tetrahydronaphthyridin-4-amine compounds as well as certain analogous thiazolo and oxazolo compounds were synthesized and found to be useful as immune response modifiers, rendering them useful in the treatment of a variety of disorders.

There continues to be interest in and a need for compounds that have the ability to modulate the immune response, by induction of cytokine biosynthesis or other mechanisms.

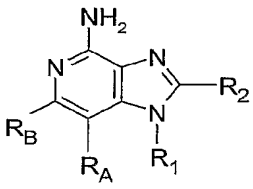
SUMMARY OF THE INVENTION

It has now been found that certain amide substituted imidazopyridine, imidazoquiniline, and imidazonaphthyridine compounds modulate cytokine biosynthesis. In one aspect, the present invention provides compounds of the Formula I:



I

and more specifically the following compounds of the Formulas II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, and XIII:



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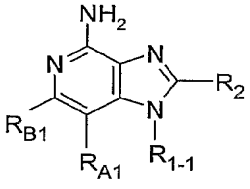

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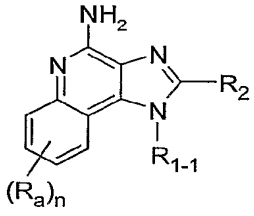

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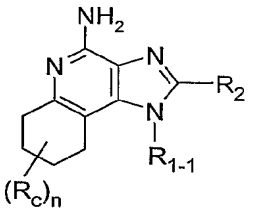

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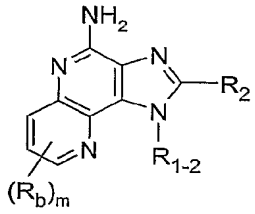

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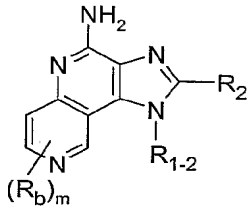

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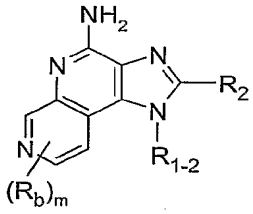

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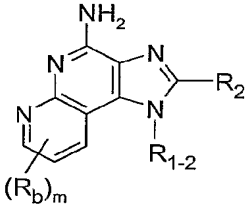

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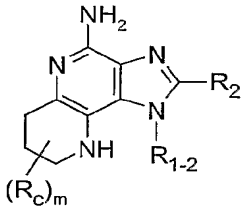

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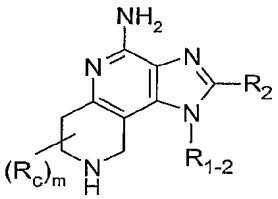

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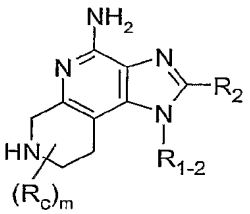

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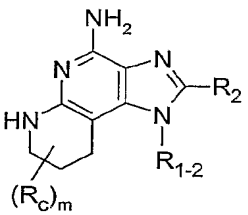


XIII

wherein R_1, $R_{1\text{-}1}$, $R_{1\text{-}2}$, R", R_2, R_A, R_B, R_{A1}, R_{B1}, R_a, R_b, R_c, n, and m are as defined below; and pharmaceutically acceptable salts thereof.

The compounds of Formulas I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, and XIII are useful, for example, as immune response modifiers (IRMs) due to their ability to modulate cytokine biosynthesis (e.g., induce the biosynthesis or production of one or more cytokines) and otherwise modulate the immune response when administered to animals. Compounds can be tested, for example, using the test procedures described in the Examples Section. Compounds can be tested for induction of cytokine biosynthesis by incubating human PBMC in a culture with the compound(s) at a concentration range of 30 to 0.014 μM and analyzing for interferon (α) or tumor necrosis factor (α) in the culture supernatant. The ability to modulate cytokine biosynthesis, for example, induce the biosynthesis of one or more cytokines, makes the compounds useful in the treatment of a variety of conditions such as viral diseases and neoplastic diseases, that are responsive to such changes in the immune response.

In another aspect, the present invention provides pharmaceutical compositions containing the immune response modifier compounds, and methods of inducing cytokine biosynthesis in animal cells, treating a viral disease in an animal, and/or treating a neoplastic disease in an animal by administering to the animal one or more compounds of the Formulas I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, and XIII, and/or pharmaceutically acceptable salts thereof.

In another aspect, the invention provides methods of synthesizing the compounds of Formulas I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, and XIII and intermediates useful in the synthesis of these compounds.

As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably.

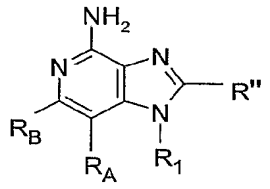
The terms "comprising" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. Guidance is also provided herein through lists of examples, which can be used in various combinations. In

each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive or exhaustive list.

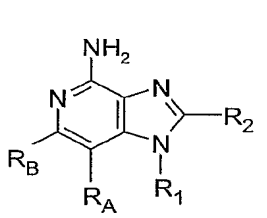
DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

In one aspect, the present invention provides compounds of the Formula I:



I

and more specifically the following compounds of the Formulas II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, and XIII:



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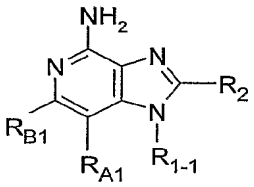

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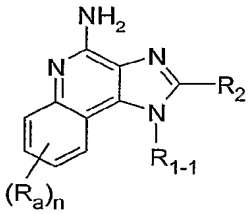

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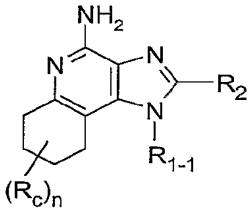

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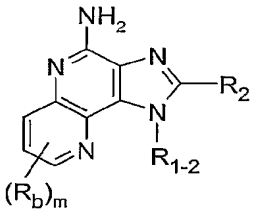

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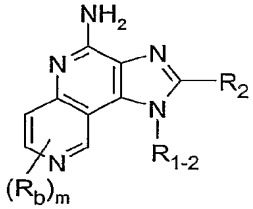

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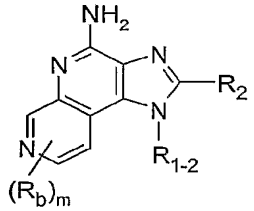

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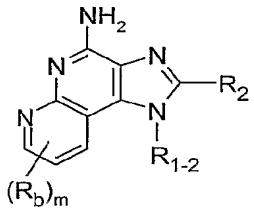

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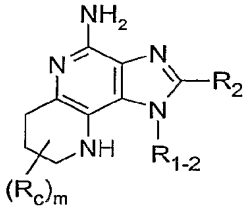

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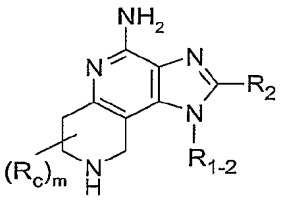

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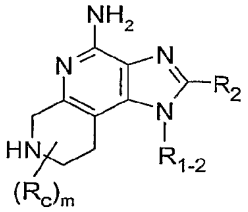

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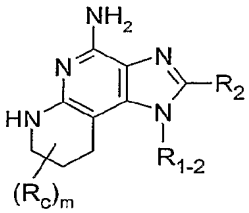
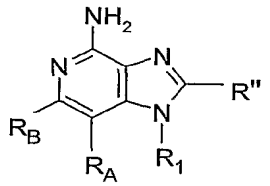


XIII

wherein R_1, R_{1-1}, R_{1-2}, R", R_2, R_A, R_B, R_{A1}, R_{B1}, R_a, R_b, R_c, n, and m are as defined below; and pharmaceutically acceptable salts thereof.

In one aspect, the present invention provides imidazopyridine, imidazoquinoline and imidazonaphthyridine compounds of the following Formula I:

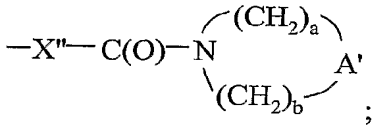


I

wherein:

R_1 is selected from the group consisting of:

$-X'-C(O)-N(R_1')(R_1")$ and



;

X' is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene-, and $-CH(R_9)$-alkenylene-;

X" is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene-, and $-CH(R_9)$-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and $R_1"$ are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
amino,
alkylamino,
dialkylamino,
arylsulfonyl, and
alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_A and R_B are independently selected from the group consisting of:

hydrogen,
halogen,
alkyl,
alkenyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

or R_A and R_B taken together form either a fused aryl ring that is unsubstituted or substituted by one or more R_a groups, or a fused 5 to 7 membered saturated ring that is unsubstituted or substituted by one or more R_c groups;

or R_A and R_B taken together form a fused heteroaryl or 5 to 7 membered saturated ring containing one heteroatom selected from the group consisting of N and S, wherein the heteroaryl ring is unsubstituted or substituted by one or more R_b groups, and the 5 to 7 membered saturated ring is unsubstituted or substituted by one or more R_c groups;

R_a is selected from the group consisting of halogen, alkyl, haloalkyl, alkoxy, and $-N(R_9)_2$;

R_b is selected from the group consisting of halogen, hydroxy, alkyl, haloalkyl, alkoxy, and $-N(R_9)_2$;

R_c is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

W is selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_6 is selected from the group consisting of =O and =S;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl; and

R" is hydrogen or a non-interfering substituent;

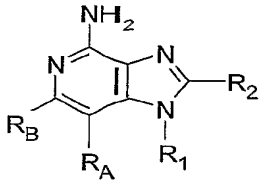
with the proviso that when R_A and R_B form a fused heteroaryl or 5 to 7 membered saturated ring containing one heteroatom selected from the group consisting of N and S, wherein the heteroaryl ring is unsubstituted or substituted by one or more R_b groups, and

the 5 to 7 membered saturated ring is unsubstituted or substituted by one or more R_c groups, then R_1 can also be -X"-C(O)-N(R_1')(R_1");

or a pharmaceutically acceptable salt thereof.

In some embodiments, compounds or salts of Formula I induce the biosynthesis of one or more cytokines.

The present invention also provides imidazopyridine, imidazoquinoline, and imidazonaphthyridine compounds of the following Formula II:

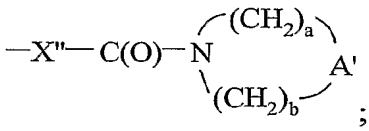


II

wherein:

R_1 is selected from the group consisting of:

-X'-C(O)-N(R_1')(R_1") and



;

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-;

X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
amino,
alkylamino,
dialkylamino,
arylsulfonyl, and
alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_A and R_B are independently selected from the group consisting of:

hydrogen,
halogen,
alkyl,
alkenyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

or R_A and R_B taken together form either a fused aryl ring that is unsubstituted or substituted by one or more R_a groups, or a fused 5 to 7 membered saturated ring that is unsubstituted or substituted by one or more R_c groups;

or R_A and R_B taken together form a fused heteroaryl or 5 to 7 membered saturated ring containing one heteroatom selected from the group consisting of N and S, wherein the heteroaryl ring is unsubstituted or substituted by one or more R_b groups, and the 5 to 7 membered saturated ring is unsubstituted or substituted by one or more R_c groups;

R_a is selected from the group consisting of halogen, alkyl, haloalkyl, alkoxy, and $-N(R_9)_2$;

R_b is selected from the group consisting of halogen, hydroxy, alkyl, haloalkyl, alkoxy, and $-N(R_9)_2$;

R_c is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

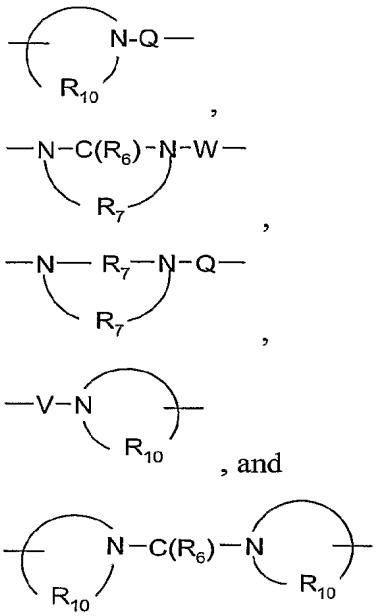
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

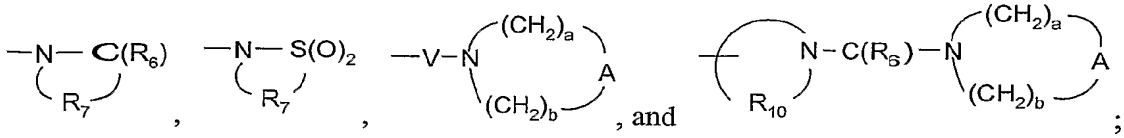
$-C(R_6)-N(OR_9)-$,



;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

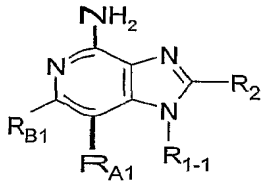
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

with the proviso that when R_A and R_B form a fused heteroaryl or 5 to 7 membered saturated ring containing one heteroatom selected from the group consisting of N and S, wherein the heteroaryl ring is unsubstituted or substituted by one or more R_b groups, and the 5 to 7 membered saturated ring is unsubstituted or substituted by one or more R_c groups, then R_1 can also be $-X''-C(O)-N(R_1')(R_1'')$;

or a pharmaceutically acceptable salt thereof.

The present invention also provides imidazopyridine compounds of the following Formula III:

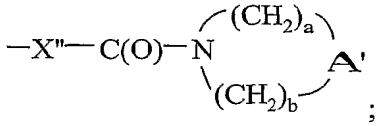


III

wherein:

R_{1-1} is selected from the group consisting of:

$-X'-C(O)-N(R_1')(R_1'')$ and



;

X' is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene-, and $-CH(R_9)$-alkenylene-;

X'' is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene-, and

-CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,

halogen,

cyano,

nitro,

amino,

alkylamino,

dialkylamino,

arylsulfonyl, and

alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, -CH_2-, -$S(O)_{0-2}$-, and -N(Q-R_4)-;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_{A1} and R_{B1} are independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

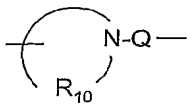
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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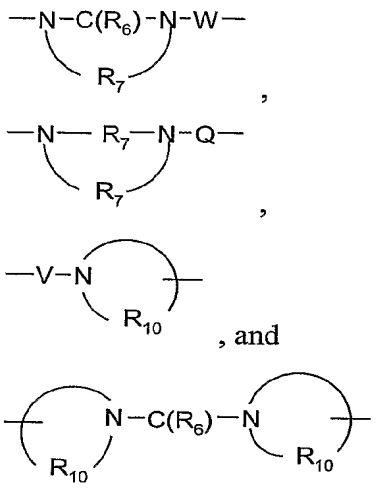
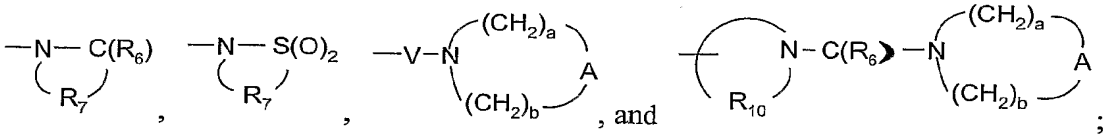


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and

$-N(R_4)-$;

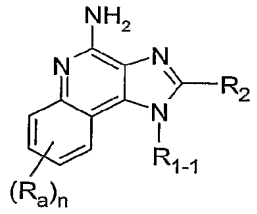
Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

The present invention also provides imidazoquinoline compounds of the following Formula IV:

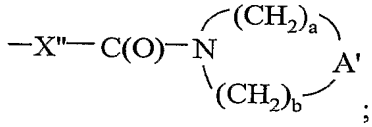


IV

wherein:

R_{1-1} is selected from the group consisting of:

$-X'-C(O)-N(R_1')(R_1'')$ and



;

X' is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene-, and $-CH(R_9)$-alkenylene-;

X" is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene-, and $-CH(R_9)$-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1'' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,

halogen,

cyano,

nitro,

amino,

alkylamino,

dialkylamino,

arylsulfonyl, and

alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$;

R_a is selected from the group consisting of halogen, alkyl, haloalkyl, alkoxy, and $-N(R_9)_2$;

n is an integer from 0 to 4;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

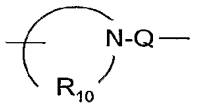
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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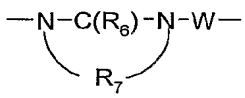

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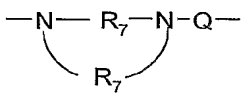

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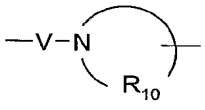

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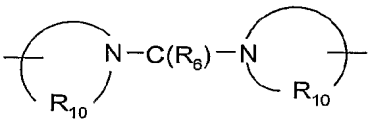
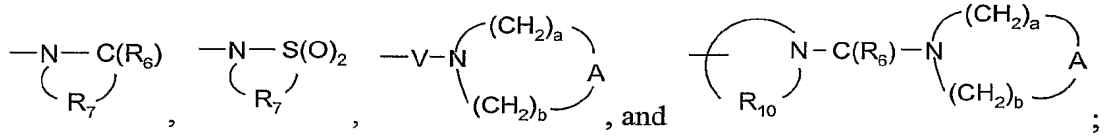


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl,

heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

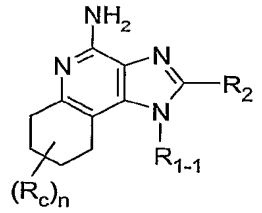
Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

The present invention also provides 6,7,8,9-tetrahydroimidazoquinoline compounds of the following Formula V:

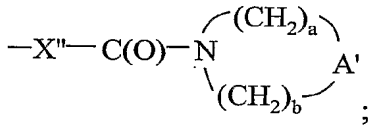


V

wherein:

R_{1-1} is selected from the group consisting of:

-X'-C(O)-N(R_1')(R_1") and



;

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-;

X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
amino,
alkylamino,
dialkylamino,
arylsulfonyl, and
alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_c is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$;

n is an integer from 0 to 4;

R_2 is selected from the group consisting of:

$-R_4$,
$-X-R_4$,
$-X-Y-R_4$, and
$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,
$-S(O)_2-N(R_8)-$,
$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

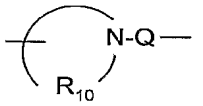
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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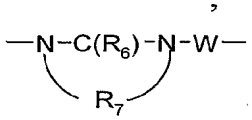

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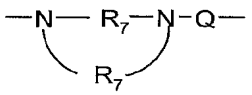

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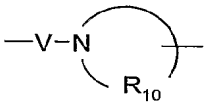

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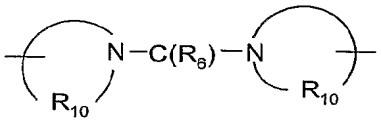
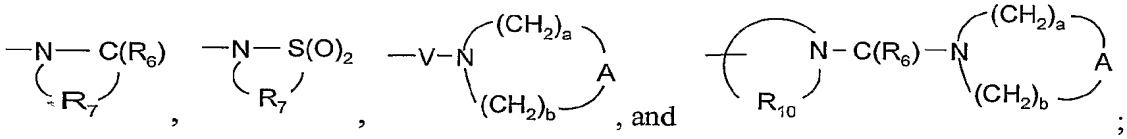


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, –C(O)-, -$S(O)_{0-2}$-, -CH_2-, and -$N(R_4)$-;

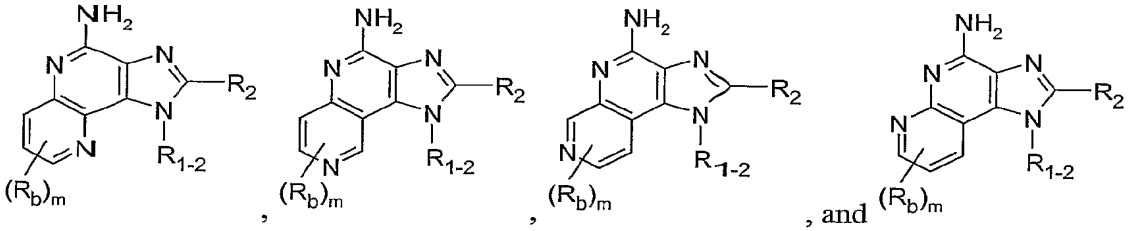
Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, and -$C(R_6)$-$N(OR_9)$-;

V is selected from the group consisting of -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-; and

W is selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-;

or a pharmaceutically acceptable salt thereof.

The present invention also provides imidazonaphthyridine compounds selected from the group consisting of the following Formulas VI, VII, VIII, and IX:

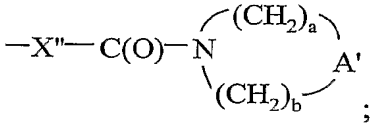


VI VII VIII IX

wherein:

R_{1-2} is selected from the group consisting of:

-X"-C(O)-$N(R_1')(R_1")$ and



X" is selected from the group consisting of -$CH(R_9)$-, -$CH(R_9)$-alkylene-, and

-CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,

halogen,

cyano,

nitro,

amino,

alkylamino,

dialkylamino,

arylsulfonyl, and

alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, -CH_2-, -$S(O)_{0-2}$-, and -N(Q-R_4)-;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_b is selected from the group consisting of halogen, hydroxy, alkyl, haloalkyl, alkoxy, and $-N(R_9)_2$;

m is an integer from 0 to 3;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

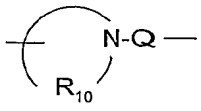
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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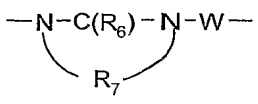

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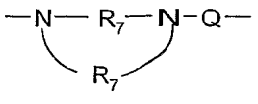

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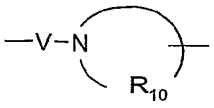
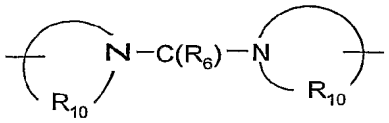
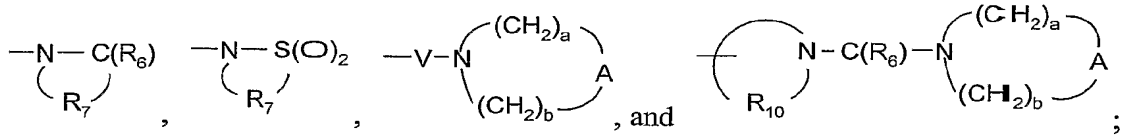

, and


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

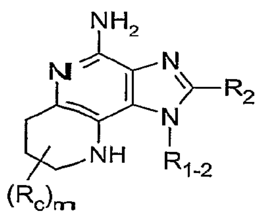
Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

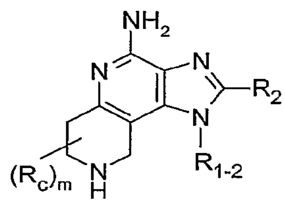
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and

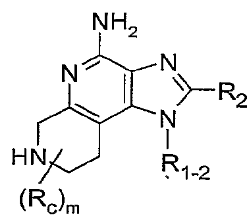
-S(O)$_2$-; and

W is selected from the group consisting of a bond, -C(O)-, and –S(O)$_2$-;
or a pharmaceutically acceptable salt thereof.

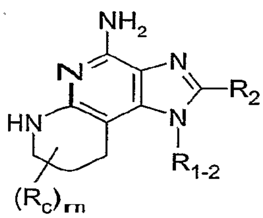
The present invention also provides 6,7,8,9-tetrahydroimidazonaphthyridine compounds selected from the group consisting of the following Formulas X, XI, XII, and XIII:


X


XI


XII

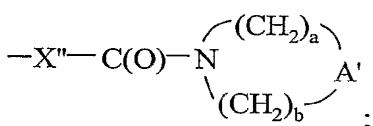
, and


XIII

wherein:

R_{1-2} is selected from the group consisting of:

-X"-C(O)-N(R_1')(R_1") and


;

X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,
alkyl,
alkenyl,
aryl,
arylalkylenyl,

heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
amino,
alkylamino,
dialkylamino,
arylsulfonyl, and
alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, -CH_2-, -$S(O)_{0-2}$-, and -$N(Q\text{-}R_4)$-;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_c is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and -$N(R_9)_2$;

m is an integer from 0 to 3;

R_2 is selected from the group consisting of:

-R_4,
-X-R_4,
-X-Y-R_4, and
-X-R_5;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

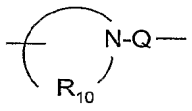
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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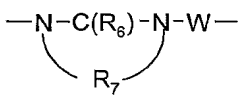

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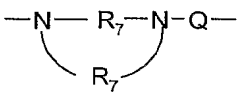

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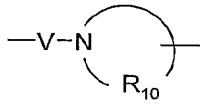
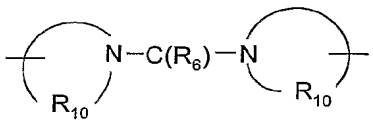


, and

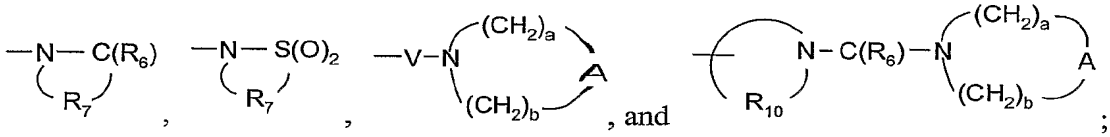


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl,

heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



, , , and ;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

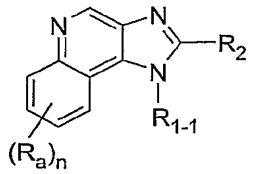
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

The present invention also provides compounds that are useful as intermediates in the synthesis of compounds of Formulas I-XIII. These intermediate compounds include those having the structural Formulas XIV, XV, and XVI described below.

The present invention provides intermediate compounds of the following Formula XIV:

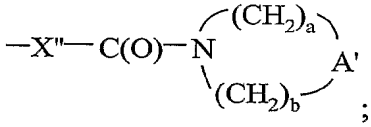


XIV

wherein:

R_{1-1} is selected from the group consisting of:

$-X'-C(O)-N(R_1')(R_1'')$ and



;

X' is selected from the group consisting of $-CH(R_9)-$, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-;

X" is selected from the group consisting of $-CH(R_9)-$, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1'' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
amino,
alkylamino,
dialkylamino,
arylsulfonyl, and
alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_a is selected from the group consisting of halogen, alkyl, haloalkyl, alkoxy, and $-N(R_9)_2$;

n is an integer from 0 to 4;

R_2 is selected from the group consisting of:

$-R_4$,
$-X-R_4$,
$-X-Y-R_4$, and
$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,
$-S(O)_2-N(R_8)-$,
$-C(R_6)-$,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

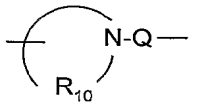
-O-C(O)-O-,

-$N(R_8)$-Q-,

-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

-$C(R_6)$-$N(OR_9)$-,



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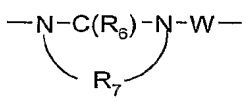

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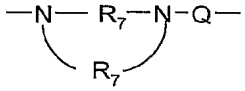

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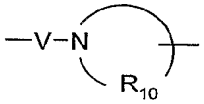
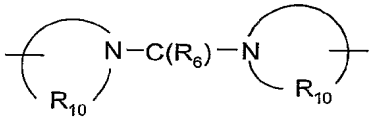


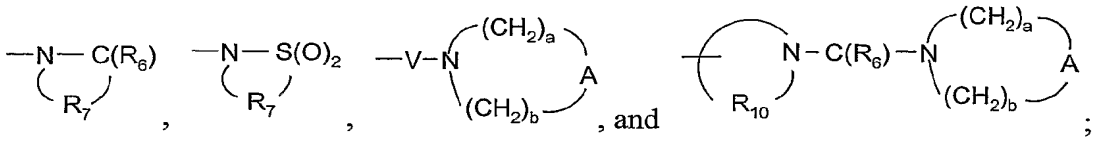
, and



;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

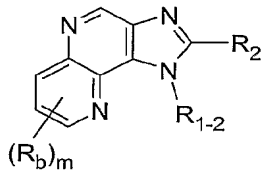
Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

The present invention provides intermediate compounds of the following Formula XV:

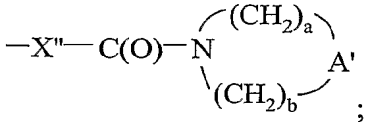


XV

wherein:

R_{1-2} is selected from the group consisting of:

$-X''-C(O)-N(R_1')(R_1'')$ and



;

X" is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene-, and

-CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,

halogen,

cyano,

nitro,

amino,

alkylamino,

dialkylamino,

arylsulfonyl, and

alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, -CH_2-, -$S(O)_{0-2}$-, and -N(Q-R_4)-;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_b is selected from the group consisting of halogen, hydroxy, alkyl, haloalkyl, alkoxy, and $-N(R_9)_2$;

m is an integer from 0 to 3;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

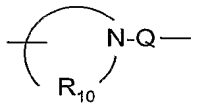
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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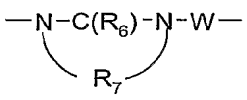

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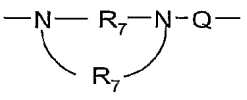

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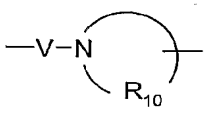

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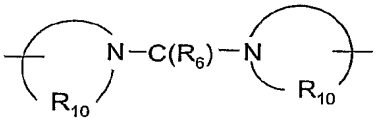
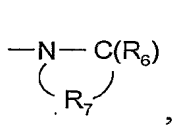


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



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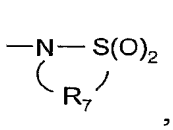

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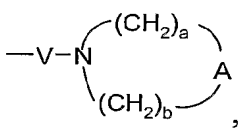
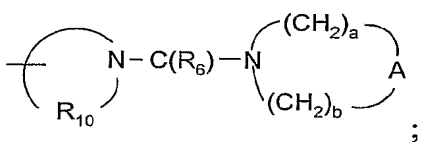


, and



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

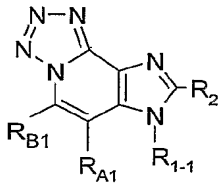
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and

$-S(O)_2-$; and

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

The present invention provides intermediate compounds of the following Formula XVI:

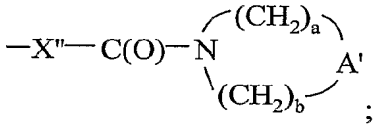


XVI

wherein:

R_{1-1} is selected from the group consisting of:

-X'-C(O)-N(R_1')(R_1") and



;

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-;

X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
amino,
alkylamino,
dialkylamino,
arylsulfonyl, and
alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_{A1} and R_{B1} are independently selected from the group consisting of:

hydrogen,
halogen,
alkyl,
alkenyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

R_2 is selected from the group consisting of:

$-R_4$,
$-X-R_4$,
$-X-Y-R_4$, and

-X-R_5;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

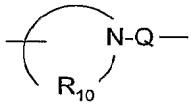
-O-C(O)-O-,

-$N(R_8)$-Q-,

-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

-$C(R_6)$-$N(OR_9)$-,



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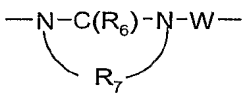

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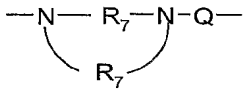

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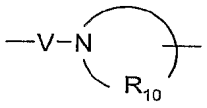

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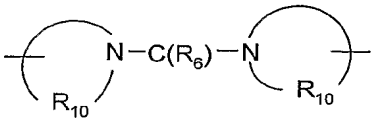
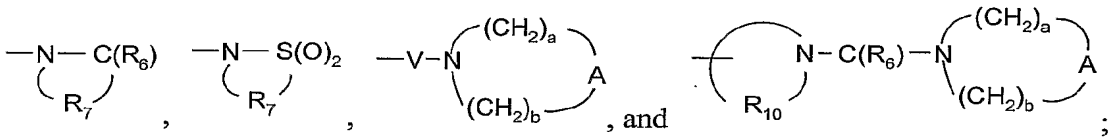


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl,

alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}$-, $-CH_2$-, and $-N(R_4)$-;

Q is selected from the group consisting of a bond, $-C(R_6)$-, $-C(R_6)-C(R_6)$-, $-S(O)_2$-, $-C(R_6)-N(R_8)-W$-, $-S(O)_2-N(R_8)$-, $-C(R_6)-O$-, and $-C(R_6)-N(OR_9)$-;

V is selected from the group consisting of $-C(R_6)$-, $-O-C(R_6)$-, $-N(R_8)-C(R_6)$-, and $-S(O)_2$-; and

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2$-;

or a pharmaceutically acceptable salt thereof.

As used herein, the terms "alkyl," "alkenyl," "alkynyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e., cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms, and alkynyl groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a

total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclohexyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene," "alkenylene," and "alkynylene" are the divalent forms of the "alkyl," "alkenyl," and "alkynyl" groups defined above. The terms "alkylenyl," "alkenylenyl," and "alkynylenyl" are used when "alkylene," "alkenylene," and "alkynylene," respectively, are substituted. For example, an arylalkylenyl group comprises an "alkylene" moiety to which an aryl group is attached.

The term "haloalkyl" is inclusive of alkyl groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of other groups that include the prefix "halo-." Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl.

The term "heteroatom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). In some embodiments, the term "heteroaryl" includes a ring or ring system that contains 2-12 carbon atoms, 1-3 rings, 1-4 heteroatoms, and O, S, and N as the heteroatoms. Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. In some embodiments, the term "heterocyclyl" includes a ring or ring system that contains 2-12 carbon atoms, 1-3 rings, 1-4 heteroatoms, and O, S, and N as the heteroatoms. Exemplary heterocyclyl groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, 1,1-

dioxothiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, tetrahydropyranyl, quinuclidinyl, homopiperidinyl (azepanyl), 1,4-oxazepanyl, homopiperazinyl (diazepanyl), 1,3-dioxolanyl, aziridinyl, azetidinyl, dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, dihydroquinolin-(2*H*)-yl, octahydroquinolin-(2*H*)-yl, dihydro-1*H*-imidazolyl, 3-azabicyclo[3.2.2]non-3-yl, and the like.

The term "heterocyclyl" includes bicylic and tricyclic heterocyclic ring systems. Such ring systems include fused and/or bridged rings and spiro rings. Fused rings can include, in addition to a saturated or partially saturated ring, an aromatic ring, for example, a benzene ring. Spiro rings include two rings joined by one spiro atom and three rings joined by two spiro atoms.

The terms "arylene," "heteroarylene," and "heterocyclylene" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. Likewise, "arylenyl," "heteroarylenyl," and "heterocyclylenyl" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

Herein, "non-interfering" means that the ability of the compound or salt, which includes a non-interfering substituent, to modulate (e.g., induce) the biosynthesis of one or more cytokines is not destroyed by the non-interfering substitutent. Illustrative non-interfering R" groups include those described above for R_2 in Formulas II-XIV.

When a group (or substituent or variable) is present more than once in any Formula described herein, each group (or substituent or variable) is independently selected, whether explicitly stated or not. For example, for the formula $-N(R_9)_2$ each R_9 group is independently selected. In another example, when an A and an A' group are both present and both contain an R_4 group, each R_4 group is independently selected. In a further example, when more than one Q group is present (i.e., R_1 and R_2 each contains a Q group) and each Q group contains one or more R_6 groups, then each Q group is independently selected, and each R_6 group is independently selected.

The invention is inclusive of the compounds described herein in any of their pharmaceutically acceptable forms, including isomers (e.g., diastereomers and enantiomers), salts, solvates, polymorphs, and the like. In particular, if a compound is optically active, the invention specifically includes each of the compound's enantiomers as

well as racemic mixtures of the enantiomers. It should be understood that the term "compound" includes any or all of such forms, whether explicitly stated or not (although at times, "salts" are explicitly stated).

For any of the compounds presented herein, each one of the following variables (e.g., R_1, R_{1-1}, R_{1-2}, R", R_2, R_A, R_B, R_{A1}, R_{B1}, R_a, R_b, R_c, n, m, and so on) in any of its embodiments can be combined with any one or more of the other variables in any of their embodiments and associated with any one of the formulas described herein, as would be understood by one of skill in the art. Each of the resulting combinations of variables is an embodiment of the present invention.

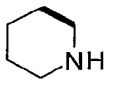
For certain embodiments, R_A and R_B are independently selected from the group consisting of: hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_A and R_B taken together form either a fused aryl ring that is unsubstituted or substituted by one or more R_a groups, or a fused 5 to 7 membered saturated ring that is unsubstituted or substituted by one or more R_c groups; or R_A and R_B taken together form a fused heteroaryl or 5 to 7 membered saturated ring containing one heteroatom selected from the group consisting of N and S, wherein the heteroaryl ring is unsubstituted or substituted by one or more R_b groups, and the 5 to 7 membered saturated ring is unsubstituted or substituted by one or more R_c groups.

The term "fused aryl ring" includes fused carbocyclic aromatic rings or ring systems. Examples of fused aryl rings include benzo, naphtho, fluoreno, and indeno. In certain embodiments, the fused aryl ring is benzo.

The term "fused heteroaryl ring" includes the fused forms of 5 or 6 membered aromatic rings that contain one heteroatom selected from S and N. In certain embodiments, the fused heteroaryl ring is pyrido or thieno. In certain embodiments, the fused heteroaryl ring is pyrido. In certain of these embodiments, the pyrido ring is 

wherein the highlighted bond indicates the position where the ring is fused.

The term "fused 5 to 7 membered saturated ring" includes rings which are fully saturated except for the bond where the ring is fused. In certain embodiments, the ring is a cyclohexene ring. In certain embodiments wherein one heteroatom (N or S) is present, the ring is tetrahydropyrido or dihydrothieno. In certain embodiments, the ring is

tetrahydropyrido. In certain of these embodiments, the ring is  wherein the highlighted bond indicates the position where the ring is fused.

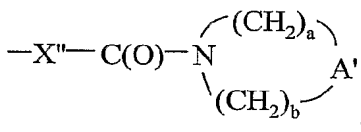
For certain embodiments, R_{A1} and R_{B1} are independently selected from the group consisting of: hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$.

For certain embodiments, R_a is selected from the group consisting of: halogen, alkyl, haloalkyl, alkoxy, and $-N(R_9)_2$.

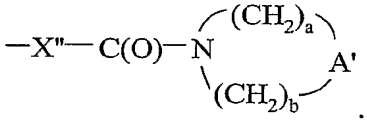
For certain embodiments, R_b is selected from the group consisting of: halogen, hydroxy, alkyl, haloalkyl, alkoxy, and $-N(R_9)_2$.

For certain embodiments, R_c is selected from the group consisting of: halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$.

For certain embodiments, R_1 is selected from the group consisting of: $-X'-C(O)-N(R_1')(R_1'')$ and



. For certain embodiments, R_1 is



. For certain embodiments R_1 is $-X'-C(O)-N(R_1')(R_1'')$.

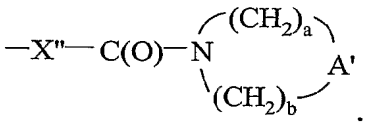
For certain embodiments, when R_A and R_B form a fused heteroaryl or 5 to 7 membered saturated ring containing one heteroatom selected from the group consisting of N and S, wherein the heteroaryl ring is unsubstituted or substituted by one or more R_b groups, and the 5 to 7 membered saturated ring is unsubstituted or substituted by one or more R_c groups, then R_1 can also be $-X''-C(O)-N(R_1')(R_1'')$.

For certain embodiments, R_1' and R_1'' are independently selected from the group consisting of: hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, heterocyclylalkylenyl, and alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of: hydroxy, alkyl, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, halogen, cyano, nitro, amino, alkylamino, dialkylamino, arylsulfonyl, and alkylsulfonyl.

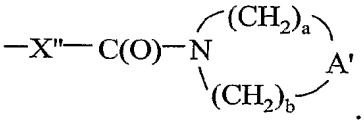
For certain embodiments, R_1' is hydrogen or C_{1-3} alkyl. For certain embodiments, R_1'' is hydrogen. For certain embodiments, R_1' and R_1'' are hydrogen. For certain embodiments, R_1' and R_1'' are methyl.

For certain embodiments, R_{1-1} is selected from the group consisting of:

-X'-C(O)-N(R_1')(R_1'') and



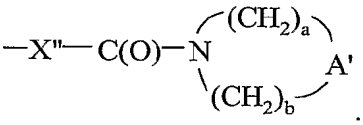
. For certain embodiments, R_{1-1} is



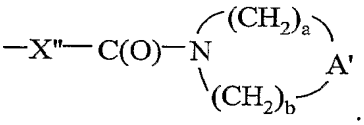
. For certain embodiments, R_{1-1} is -X'-C(O)-N(R_1')(R_1'').

For certain embodiments, R_{1-2} is selected from the group consisting of:

-X''-C(O)-N(R_1')(R_1'') and



. For certain embodiments, R_{1-2} is



. For certain embodiments, R_{1-2} is –X''-C(O)-N(R_1')(R_1'').

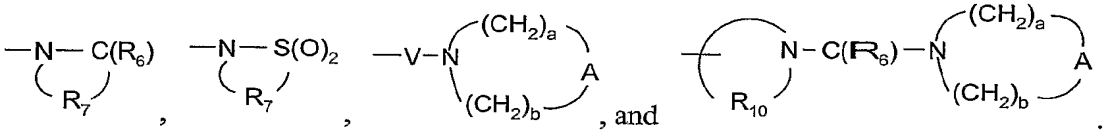
For certain embodiments, R'' is hydrogen or a non-interfering substituent. For certain embodiments, R'' is R_2.

For certain embodiments, R_2 is selected from the group consisting of: -R_4, -X-R_4, -X-Y-R_4, and -X-R_5. For certain embodiments, R_2 is hydrogen, alkoxyalkylenyl, hydroxyalkylenyl, -R_4, -X-R_4, or -X-Y-R_4. For certain embodiments, R_2 is hydrogen, alkoxyalkylenyl, -R_4, -X-R_4, or -X-Y-R_4. For certain embodiments, R_2 is hydrogen, C_{1-4} alkyl, hydroxyC_{1-4} alkylenyl, or C_{1-4} alkyl-O-C_{1-4} alkylenyl. For certain embodiments, R_2 is hydrogen, C_{1-4} alkyl, or C_{1-4} alkyl-O-C_{1-4} alkylenyl. For certain embodiments, R_2 is hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, ethoxymethyl, hydroxymethyl, or 2-hydroxyethyl. For certain embodiments, R_2 is hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, or ethoxymethyl. For certain embodiments, R_2 is methyl, ethyl, propyl, butyl, 2-methoxyethyl, or ethoxymethyl.

For certain embodiments, R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl,

heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo. In certain embodiments, R_4 is alkyl. In certain embodiments, R_4 is methyl.

For certain embodiments, R_5 is selected from the group consisting of:



For certain embodiments, R_6 is selected from the group consisting of =O and =S. For certain embodiments, R_6 is =O.

For certain embodiments, R_7 is C_{2-7} alkylene.

For certain embodiments, R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl.

For certain embodiments, R_9 is selected from the group consisting of hydrogen and alkyl.

For certain embodiments, R_{10} is C_{3-8} alkylene.

For certain embodiments, A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}$-, $-CH_2$-, and $-N(R_4)$-.

For certain embodiments, A' is selected from the group consisting of -O-, -C(O)-, $-CH_2$-, $-S(O)_{0-2}$-, and $-N(Q-R_4)$-. For certain embodiments, A' is $-SO_2$-, -O-, or $-N(Q-R_4)$-. For certain embodiments, A' is -O- or $-N(Q-R_4)$-. For certain embodiments, A' is -O-. In certain embodiments, A' is $-CH_2$-

For certain embodiments, Q is selected from the group consisting of a bond, $-C(R_6)$-, $-C(R_6)-C(R_6)$-, $-S(O)_2$-, $-C(R_6)-N(R_8)-W$-, $-S(O)_2-N(R_8)$-, $-C(R_6)-O$-, and $-C(R_6)-N(OR_9)$-. For certain embodimentds, Q is -C(O)-.

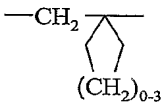
For certain embodiments, V is selected from the group consisting of $-C(R_6)$-,

-O-C(R_6)-, -N(R_8)-C(R_6)-, and -S(O)$_2$-.

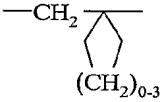
For certain embodiments, W is selected from the group consisting of a bond, -C(O)-, and -S(O)$_2$-.

For certain embodiments, X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups. For certain embodiments, X is C_{1-2} alkylene.

For certain embodiments, X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-. For certain embodiments, X' is -CH_2-C_{0-10} alkylene-. For certain embodiments, X' is -CH_2-C_{0-4} alkylene-. For certain embodiments, X' is -$(CH_2)_{1-5}$-, -$CH_2C(CH_3)_2$-, or -$CH_2C(CH_3)_2CH_2$-. For certain embodiments, X' is -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-,-$CH_2C(CH_3)_2$-, -$CH_2C(CH_3)_2CH_2$-, or

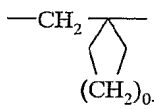


. For certain embodiments, X' is -CH_2-, -CH_2CH_2-, -$CH_2C(CH_3)_2$-, or

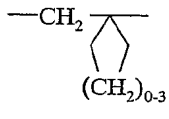


. For certain embodiments, X' is -CH_2CH_2- or -$CH_2C(CH_3)_2$-.

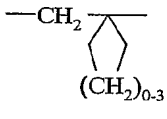
For certain embodiments, X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups. For certain embodiments, X" is -CH_2-C_{0-10} alkylene- or -CH_2-C_{1-4} alkylene-O-C_{1-4} alkylene-. For certain embodiments, X" is -CH_2-C_{0-4} alkylene- or -CH_2-C_{1-4} alkylene-O-C_{1-4} alkylene-. For certain embodiments, X" is -$(CH_2)_{1-5}$-, -$CH_2C(CH_3)_2$-, -$CH_2C(CH_3)_2CH_2$-, or -$(CH_2)_3$-O-CH_2-. For certain embodiments, X" is -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH_2C(CH_3)_2$-, -$CH_2C(CH_3)_2CH_2$-, or

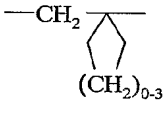


. For certain embodiments, X" is -CH_2-, -CH_2CH_2-, -$CH_2C(CH_3)_2$-, or

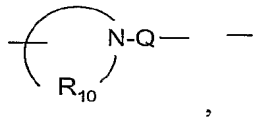

. For certain embodiments, X" is $-CH_2CH_2-$ or $-CH_2C(CH_3)_2-$.

For certain embodiments, X' or X" is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2C(CH_3)_2-$, $-CH_2C(CH_3)_2CH_2-$, or


. For certain embodiments, X' or X" is $-CH_2-$, $-CH_2CH_2-$, $-CH_2C(CH_3)_2-$, or


. For certain embodiments, X' or X" is $-CH_2CH_2-$ or $-CH_2C(CH_3)_2-$.

For certain embodiments, Y is selected from the group consisting of: $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, $-O-C(O)-O-$, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, $-C(R_6)-N(OR_9)-$,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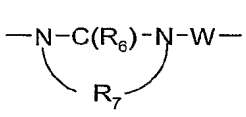
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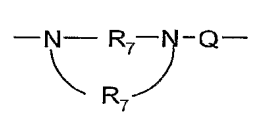
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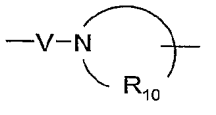
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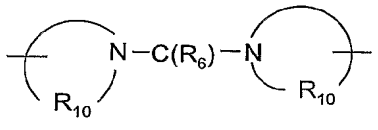

.

For certain embodiments, Y is $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, $-O-C(O)-O-$, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, or $-C(R_6)-N(OR_9)-$.

For certain embodiments, a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7. For certain embodiments, a and b are independently integers from 1 to 3. For certain embodiments, a and b are independently integers from 2 to 3. For certain embodiments, a and b are each 2.

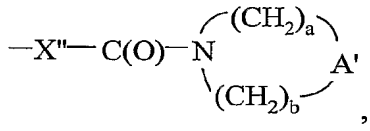
For certain embodiments, m is an integer from 0 to 3. For certain embodiments, m is 0.

For certain embodiments, n is an integer from 0 to 4. For certain embodiments, n is 0.

In some embodiments, particularly embodiments of Formulas I and II, and more particularly embodiments of Formula II, the fused aryl ring, fused heteroaryl ring, fused 5 to 7 membered saturated ring, or fused 5 to 7 membered saturated ring containing one N or S atom is unsubstituted.

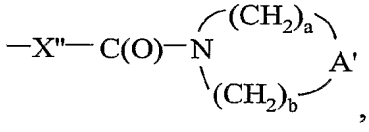
In some embodiments, particularly embodiments of Formula III, R_{A1} and R_{B1} are methyl.

In some embodiments, particularly embodiments of Formula II, R_1 is



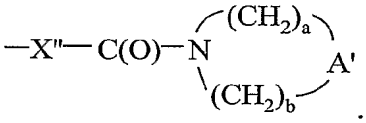
, A' is -O- or -N(Q-R_4)-, and a and b are independently integers from 2 to 3; or A' is -CH_2-, and a and b are independently integers from 1 to 3.

In some embodiments, particularly embodiments of Formula II, R_1 is



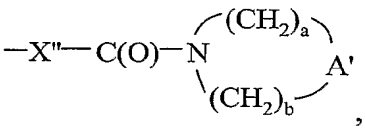
, A' is -SO_2-, -O-, or -N(Q-R_4)-, and a and b are independently integers from 2 to 3; or A' is -CH_2-, and a and b are independently integers from 1 to 3.

In some embodiments, particularly embodiments of Formulas III, IV, and V, $R_{1\text{-}1}$ is



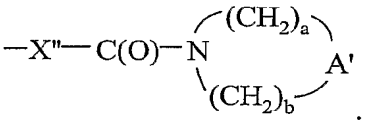
.

In some embodiments, particularly embodiments of Formulas III, IV, and V, $R_{1\text{-}1}$ is



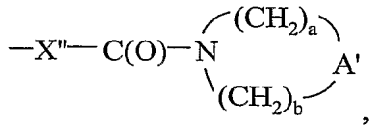
, A' is -O-, and a and b are each 2.

In some embodiments, particularly embodiments of Formulas VI through XIII, and more particularly embodiments of Formulas VI through IX, $R_{1\text{-}2}$ is



.

In some embodiments, particularly embodiments of Formulas VI through XIII, and more particularly embodiments of Formulas VI through IX, $R_{1\text{-}2}$ is


, A' is -O-, and a and b are each 2.

In some embodiments, particularly embodiments of Formulas III through XIII, and more particularly embodiments of Formulas III through IX, R_1' is hydrogen or C_{1-3} alkyl, and R_1'' is hydrogen. In some embodiments, particularly embodiments of Formula II, R_1' is hydrogen or C_{1-3} alkyl.

In some embodiments, particularly embodiments of Formulas III through XIII, and more particularly embodiments of Formulas III through IX, R_1' and R_1'' are hydrogen. In some embodiments, particularly embodiments of Formula II, R_1'' is hydrogen.

In some embodiments, particularly embodiments of Formulas II through XIII, and more particularly embodiments of Formulas II through IX, R_1' and R_1'' are methyl.

In some embodiments, particularly embodiments of Formulas II through XIII, and more particularly embodiments of Formulas II through IX, R_2 is hydrogen, alkoxyalkylenyl, $-R_4$, $-X-R_4$, or $-X-Y-R_4$; X is C_{1-2} alkylene; Y is $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, $-O-C(O)-O-$, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, or $-C(R_6)-N(OR_9)-$; and R_4 is alkyl. In some embodiments, particularly embodiments of Formulas II through XIII, and more particularly embodiments of Formulas II through IX, R_2 is hydrogen, C_{1-4} alkyl, or C_{1-4} alkyl-O-C_{1-4} alkylenyl. In some embodiments, particularly embodiments of Formulas II through XIII, and more particularly embodiments of Formulas II through IX, R_2 is hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, or ethoxymethyl.

In some embodiments, particularly embodiments of Formulas II through XIII, and more particularly embodiments of Formulas II through IX, R_2 is hydrogen, alkoxyalkylenyl, hydroxyalkylenyl, $-R_4$, $-X-R_4$, or $-X-Y-R_4$; X is C_{1-2} alkylene; Y is $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, $-O-C(O)-O-$, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, or $-C(R_6)-N(OR_9)-$; and R_4 is alkyl. In some embodiments, particularly embodiments of Formulas II through XIII, and more particularly embodiments of Formulas II through IX, R_2 is hydrogen, C_{1-4} alkyl, hydroxyC_{1-4} alkylenyl, or C_{1-4} alkyl-O-C_{1-4} alkylenyl. In some embodiments, particularly embodiments of Formulas II through XIII, and more particularly embodiments

of Formulas II through IX, R_2 is hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, ethoxymethyl, hydroxymethyl, or 2-hydroxyethyl.

In some embodiments, particularly embodiments of Formula II, A' is -O- or -N(Q-R_4)-, and a and b are independently integers from 2 to 3; or A' is -CH_2-, and a and b are independently integers from 1 to 3.

In some embodiments, particularly embodiments of Formulas I through XIII, more particularly embodiments of Formulas I through IX, and more particularly embodiments of Formulas II through IX, A' is -SO_2-, -O-, or -N(Q-R_4)-, and a and b are independently integers from 2 to 3; or A' is -CH_2-, and a and b are independently integers from 1 to 3.

In some embodiments, particularly embodiments of Formulas III through XIII, and more particularly embodiments of Formulas III through IX, A' is -O-, and a and b are each 2.

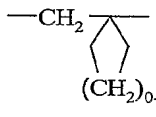
In some embodiments, particularly embodiments of Formula I, X' is -CH_2-C_{0-10} alkylene- or X" is -CH_2-C_{0-10} alkylene- or -CH_2-C_{1-4} alkylene-O-C_{1-4} alkylene-. In some embodiments, particularly embodiments of Formulas II through V, X' is -CH_2-C_{0-4} alkylene- or X" is -CH_2-C_{0-4} alkylene- or -CH_2-C_{1-4} alkylene-O-C_{1-4} alkylene-.

In some embodiments, particularly embodiments of Formulas II through V, and more particularly embodiments of Formulas III through V, X' is -$(CH_2)_{1-5}$-, -$CH_2C(CH_3)_2$-, or -$CH_2C(CH_3)_2CH_2$-; or X" is -$(CH_2)_{1-5}$-, -$CH_2C(CH_3)_2$-, -$CH_2C(CH_3)_2CH_2$-, or -$(CH_2)_3$-O-CH_2-.

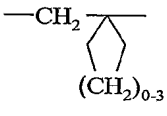
In some embodiments, particularly embodiments of Formulas II through V, X' or X" is -CH_2CH_2- or -$CH_2C(CH_3)_2$-.

In some embodiments, X" is -CH_2-C_{0-10} alkylene- or -CH_2-C_{1-4} alkylene-O-C_{1-4} alkylene-. In some embodiments, particularly embodiments of Formulas VI through XIII, and more particularly embodiments of Formulas VI through IX, X" is -CH_2-C_{0-4} alkylene- or -CH_2-C_{1-4} alkylene-O-C_{1-4} alkylene-. In some embodiments, particularly embodiments of Formulas VI through XIII, and more particularly embodiments of Formulas VI through IX, X" is -$(CH_2)_{1-5}$-, -$CH_2C(CH_3)_2$-, -$CH_2C(CH_3)_2CH_2$-, or -$(CH_2)_3$-O-CH_2-. In some embodiments, particularly embodiments of Formulas VI through XIII, and more particularly embodiments of Formulas VI through IX, X" is -CH_2CH_2- or -$CH_2C(CH_3)_2$-.

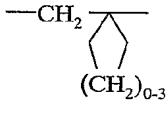
In some embodiments, particularly embodiments of Formulas I through V, more particularly embodiments of Formulas III through V, X' or X" is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$,$-CH_2C(CH_3)_2-$, $-CH_2C(CH_3)_2CH_2-$, or



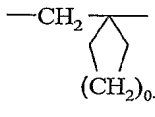
In some embodiments, particularly embodiments of Formulas I through V, more particularly embodiments of Formulas III through V, X' or X" is $-CH_2-$, $-CH_2CH_2-$, $-CH_2C(CH_3)_2-$, or



In some embodiments, particularly embodiments of Formulas VI through XIII, more particularly embodiments of Formulas VI through IX, X" is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$,$-CH_2C(CH_3)_2-$, $-CH_2C(CH_3)_2CH_2-$, or



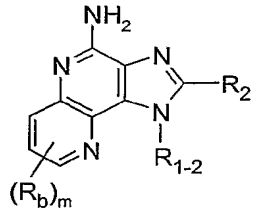
In some embodiments, particularly embodiments of Formulas VI through XIII, more particularly embodiments of Formulas VI through IX, X" is $-CH_2-$, $-CH_2CH_2-$, $-CH_2C(CH_3)_2-$, or



In some embodiments, particularly embodiments of Formulas VI through XIII, and more particularly embodiments of Formulas VI through IX, m is 0.

In some embodiments, particularly embodiments of Formulas IV and V, n is 0.

In some embodiments the imidazonaphthyridine compounds are of the following Formula VI:



VI,

or a pharmaceutically acceptable salt thereof.

In some embodiments, particularly embodiments of Formula II, R_1 is $-CH_2CH_2C(O)NH_2$ or $-CH_2C(CH_3)_2-C(O)NH_2$.

In some embodiments, particularly embodiments of Formulas III through V, R_{1-1} is $-CH_2CH_2C(O)NH_2$ or $-CH_2C(CH_3)_2-C(O)NH_2$.

In some embodiments, particularly embodiments of Formulas VI through XIII, more particularly embodiments of Formulas VI through IX, R_{1-2} is $-CH_2CH_2C(O)NH_2$ or $-CH_2C(CH_3)_2-C(O)NH_2$.

In some embodiments, particularly embodiments of Formula II, R_1 is $-CH_2CH_2C(O)NH_2$ or $-CH_2C(CH_3)_2-C(O)NH_2$, and R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, ethoxymethyl, 2-methoxyethyl, hydroxymethyl, and 2-hydroxyethyl.

In some embodiments, particularly embodiments of Formulas III through V, R_{1-1} is $-CH_2CH_2C(O)NH_2$ or $-CH_2C(CH_3)_2-C(O)NH_2$, and R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, ethoxymethyl, 2-methoxyethyl, hydroxymethyl, and 2-hydroxyethyl.

In some embodiments, particularly embodiments of Formulas VI through XIII, more particularly embodiments of Formulas VI through IX, R_{1-2} is $-CH_2CH_2C(O)NH_2$ or $-CH_2C(CH_3)_2-C(O)NH_2$, and R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, ethoxymethyl, 2-methoxyethyl, hydroxymethyl, and 2-hydroxyethyl.

Preparation of the Compounds

Compounds of Formula IVa can be prepared according to Reaction Scheme I, wherein R_a and n are as defined above, X_a is either X' or X", and $R_{1\text{-}1a}$ and R_{2a} are subsets of $R_{1\text{-}1}$ and R_2 as defined above that do not include those substituents that one skilled in the art would recognize as being susceptible to oxidation in step (5). These substituents include -S- and heteroaryl groups. In step (1) of Reaction Scheme I, a 4-chloro-3-nitroquinoline of Formula XX is reacted with an amino ester of the Formula $H_2N\text{-}X_a\text{-}C(O)\text{-}O\text{-}$alkyl or a hydrochloride salt thereof to form a compound of Formula XXI. This reaction is conveniently carried out by adding a compound of the Formula $H_2N\text{-}X_a\text{-}C(O)\text{-}O\text{-}$alkyl - HCl to a solution of a 4-chloro-3-nitroquinoline of Formula XX in the presence of a base such as triethylamine, potassium carbonate, or a combination thereof. The reaction is carried out in a suitable solvent, such as dichloromethane or chloroform. Compounds of the Formula $H_2N\text{-}X_a\text{-}C(O)\text{-}O\text{-}$alkyl - HCl can be commercially obtained or readily synthesized using conventional methods. For example, the amino ester wherein -alkyl is ethyl and X_a is butylene or dodecylene can be synthesized according to the procedure of C. Temple et al., *J. Med. Chem.*, *31*, pp. 697-700 (1988). Many compounds of Formula XX are known or can be prepared using known synthetic methods, see for example, U.S. Patent Nos. 4,689,338; 5,175,296; 5,367,076; and 5,389,640; and the documents cited therein.

The resultant compound of Formula XXI can be reduced in step (2) of Reaction Scheme I using a variety of methods to provide a quinoline-3,4-diamine of Formula XXII. The reaction can be carried out by hydrogenation using a heterogeneous hydrogenation catalyst such as platinum on carbon. The hydrogenation is conveniently carried out in a Parr apparatus in a suitable solvent such as toluene or ethanol. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

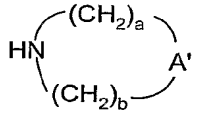
Alternatively step (2) can be carried out using a one- or two-phase sodium dithionite reduction. The reaction is conveniently carried out using the conditions described by Park, K. K.; Oh, C. H.; and Joung, W. K.; *Tetrahedron Lett.*, *34*, pp. 7445-7446 (1993) by adding sodium dithionite to a compound of Formula XXI in a mixture of dichloromethane and water at ambient temperature in the presence of potassium carbonate and ethyl viologen dibromide, ethyl viologen diiodide, or 1,1'-di-*n*-octyl-4,4'-bipyridinium dibromide. The product can be isolated using conventional methods.

In step (3) of Reaction Scheme I, a quinoline-3,4-diamine of Formula XXII is treated with a carboxylic acid or equivalent thereof to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXIII. Suitable carboxylic acid equivalents include orthoesters of Formula $R_{2a}C(O\text{-alkyl})_3$, 1,1-dialkoxyalkyl alkanoates of Formula $R_{2a}C(O\text{-alkyl})_2(O\text{-}C(O)\text{-alkyl})$, and acid chlorides of Formula $R_{2a}C(O)Cl$. The selection of the carboxylic acid equivalent is determined by the desired substituent at R_{2a}. For example, triethyl orthoformate will provide a compound where R_{2a} is hydrogen, and trimethyl orthovalerate will provide a compound where R_{2a} is a butyl group. The reaction is conveniently carried out by adding the carboxylic acid equivalent to a quinoline-3,4-diamine of Formula XXII in a suitable solvent such as toluene. Optionally, catalytic pyridine hydrochloride or pyridinium *p*-toluenesulfonate can be added. The reaction is carried out at a temperature high enough to drive off alcohol or water formed during the reaction. Conveniently, a Dean-Stark trap can be used to collect the volatiles.

Alternatively, step (3) can be carried out in two steps when an acid chloride of Formula $R_{2a}C(O)Cl$ is used as the carboxylic acid equivalent. The first step is conveniently carried out by adding the acid chloride to a solution of a quinoline-3,4-diamine of Formula XXII in a suitable solvent such as dichloromethane to afford an amide. Optionally, a tertiary amine such as triethylamine, pyridine, or 4-dimethylaminopyridine can be added. The reaction can be carried out at ambient temperature. The amide product can be isolated and optionally purified using conventional techniques before it is heated and cyclized to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXIII. The cyclization reaction is conveniently carried out in a solvent such as ethanol or methanol in the presence of a base such as triethylamine and may be carried out at an elevated temperature, such as the reflux temperature of the solvent. The 1*H*-imidazo[4,5-*c*]quinoline of Formula XXIII can be isolated using conventional methods.

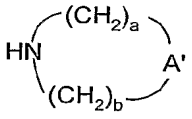
In step (4) or steps (4a) and (4b) of Reaction Scheme I, the ester group of a 1*H*-imidazo[4,5-*c*]quinoline Formula XXIII is converted to an amide to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XIVa. The transformation can be carried out by base-promoted hydrolysis of the ester in step (4a) to form a carboxylic acid of Formula XXIV. In step (4b), a carboxylic acid of Formula XXIV is converted to an acid chloride using conventional methods and then treated with an amine to provide an amide-substituted 1*H*-

imidazo[4,5-*c*]quinoline of Formula XIVa. The base-promoted hydrolysis in step (4a) is conveniently carried out by adding sodium hydroxide to an ester-substituted 1*H*-imidazo[4,5-*c*]quinoline Formula XXIII in a suitable solvent such as ethanol. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods. The conversion of the resulting carboxylic acid to an acid chloride is conveniently carried out by slowly adding oxalyl chloride to a solution of the carboxylic acid in a suitable solvent such as dichloromethane. The reaction can be carried out at a sub-ambient temperature, such as 0 °C, or at ambient temperature. The resulting acid chloride can then be treated with an amine of Formula $HN(R_1')(R_1'')$ or

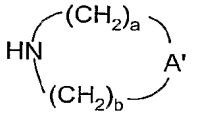


in a suitable solvent such as dichloromethane. Numerous amines of these formulas are commercially available; others can be prepared by known synthetic methods. The reaction can be run at ambient temperature, and the product of Formula XIVa or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Alternatively, step (4) can be used to convert an ester-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XXIII to an amide of Formula XIVa in one step by treating the compound Formula XXIII with an amine of Formula $HN(R_1')(R_1'')$ or

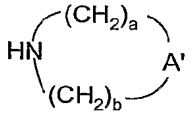


or a hydrochloride salt thereof in the presence of trimethylaluminum. The reaction is conveniently carried out by adding a solution of an ester-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XXIII in a suitable solvent such as dichloromethane to a pre-reacted mixture of trimethylaluminum and an amine of Formula $HN(R_1')(R_1'')$ or



or a hydrochloride salt thereof in a suitable solvent such as dichloromethane. The reaction can then be heated at an elevated temperature, for example, the reflux temperature of the solvent. The product can be isolated using conventional methods.

Step (4) of Reaction Scheme I can also be carried out by heating an ester-substituted 1*H*-imidazo[4,5-*c*]quinoline Formula XXIII in the presence of an amine of Formula $HN(R_1')(R_1'')$ or



at an elevated temperature such as 90-120 °C. The reaction is conveniently carried out in a high-pressure vessel and can be run neat or in a suitable solvent such as tetrahydrofuran (THF). An ester of Formula XXIII can be heated in the presence of ammonium acetate at an elevated temperature such as 110 to 140 °C to provide a compound of Formula XIVa, where

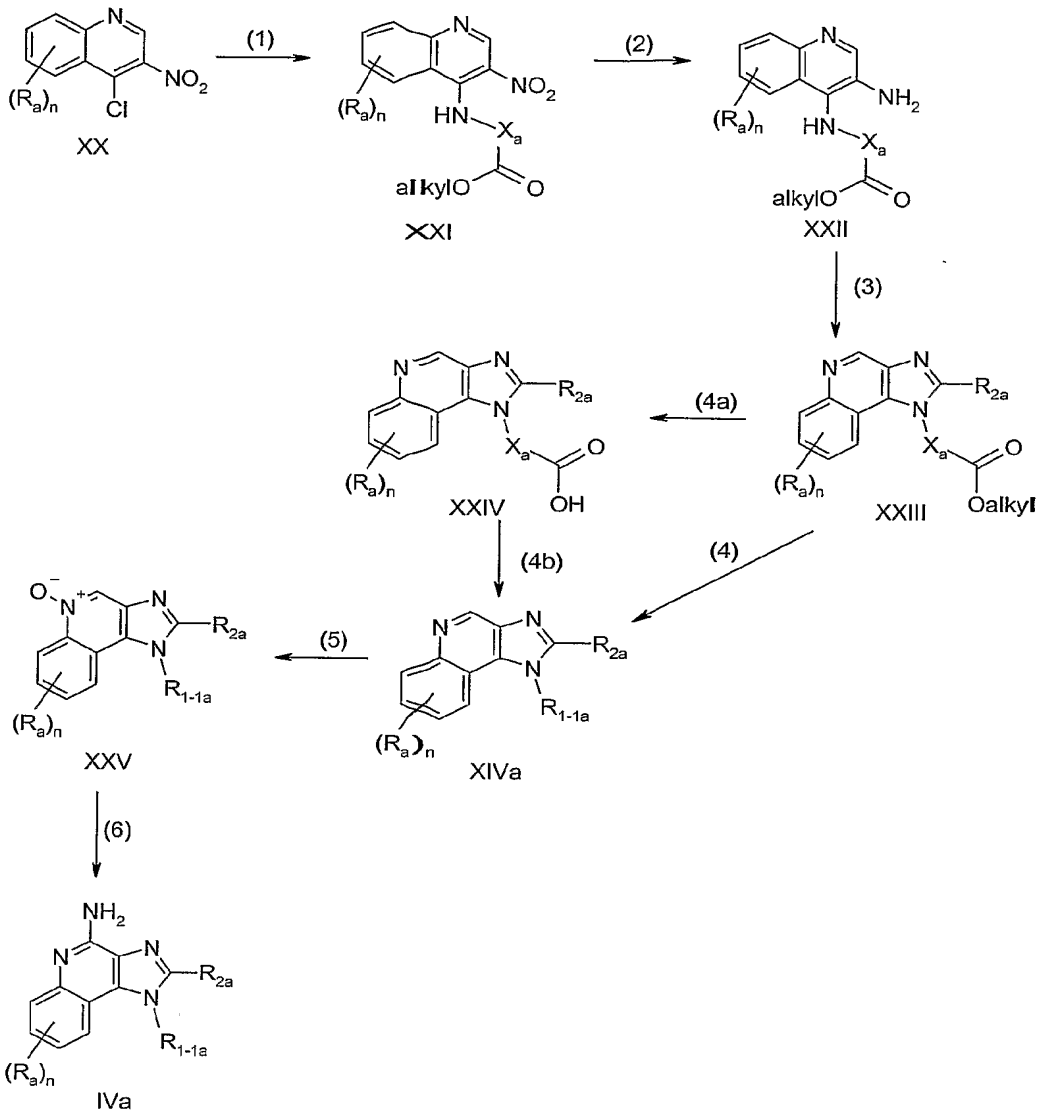
$R_{1\text{-}1a}$ is -X'-C(O)-NH_2. The product can be isolated by conventional methods.

In step (5) of Reaction Scheme I, an amide-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XIVa is oxidized to provide a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XXV using a conventional oxidizing agent capable of forming *N*-oxides. The reaction is conveniently carried out by adding 3-chloroperoxybenzoic acid to a solution of a compound of Formula XIVa in a solvent such as dichloromethane or chloroform. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

In step (6) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XXV is aminated to provide an amide-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula IVa, a subgenus of Formulas I, II, and IV. Step (6) can be carried out by the activation of an *N*-oxide of Formula XXV by conversion to an ester and then reacting the ester with an aminating agent. Suitable activating agents include alkyl- or arylsulfonyl chlorides such as benzenesulfonyl chloride, methanesulfonyl chloride, or *p*-toluenesulfonyl chloride. Suitable aminating agents include ammonia, in the form of ammonium hydroxide, for example, and ammonium salts such as ammonium carbonate, ammonium bicarbonate, and ammonium phosphate. The reaction is conveniently carried out by adding ammonium hydroxide to a solution of the *N*-oxide of Formula XXV in a suitable solvent such as dichloromethane or chloroform and then adding *p*-toluenesulfonyl chloride. The reaction can be carried out at ambient temperature. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

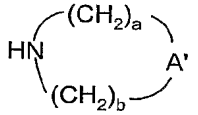
Steps (5) and (6) of Reaction Scheme I may be carried out as a one-pot procedure by adding 3-chloroperoxybenzoic acid to a solution of a compound of Formula XIVa in a solvent such as dichloromethane or chloroform and then adding ammonium hydroxide and *p*-toluenesulfonyl chloride without isolating the *N*-oxide compound of Formula XXV. The product of Formula IVa or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Reaction Scheme I



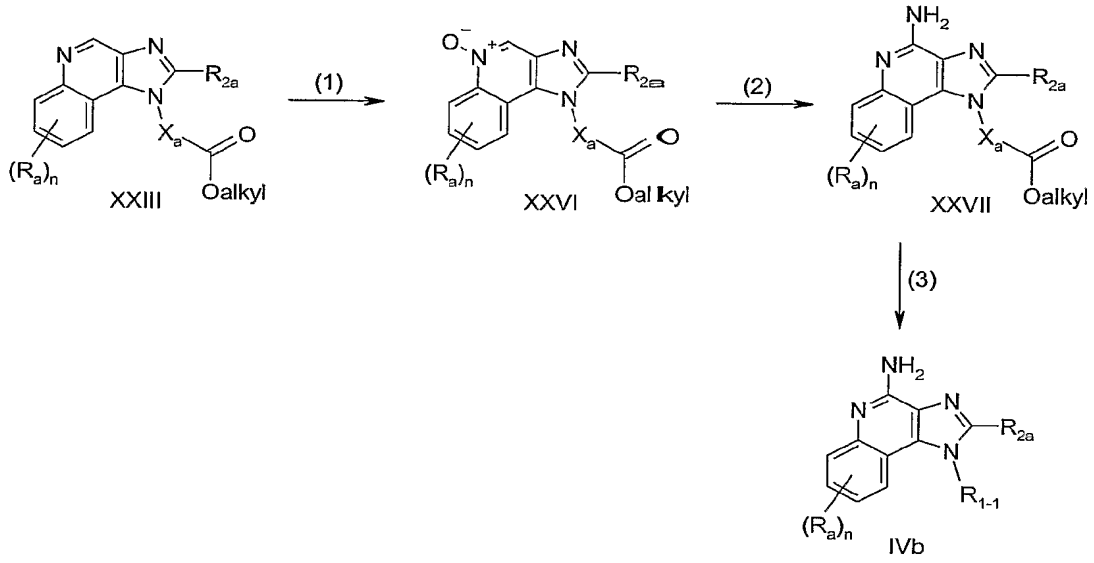
Compounds of the invention can also be prepared according to Reaction Scheme II, wherein R_a, R_{2a}, $R_{1\text{-}1}$, X_a, and n are as defined above. In step (1) of Reaction Scheme II, an ester-substituted 1*H*-imidazo[4,5-*c*]quinoline Formula XXIII is oxidized to an *N*-oxide of Formula XXVI, which is then aminated in step (2) to provide an ester-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine Formula XXVII. Steps (1) and (2) of Reaction Scheme II can be carried out as described for steps (5) and (6) of Reaction Scheme I.

In step (3) of Reaction Scheme II, an ester-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine Formula XXVII is heated in the presence of an amine of Formula $HN(R_1')(R_1")$ or



at an elevated temperature such as 90-120 °C to provide an amide-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine Formula IVb, a subgenus of Formulas I, II, and IV. The reaction is conveniently carried out in a high-pressure vessel and can be run neat or in a suitable solvent such as THF. An ester of Formula XXVII can be heated in the presence of ammonium acetate at an elevated temperature such as 110 to 140 °C to provide a compound of Formula IVb, where R_{1-1} is $-X_a-C(O)-NH_2$. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

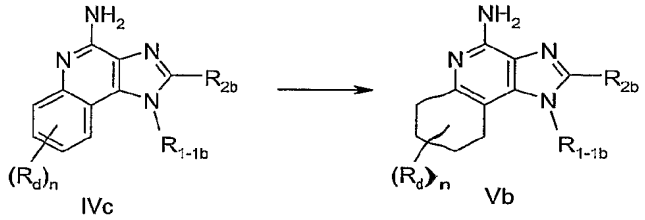
Reaction Scheme II



Compounds of the invention can also be prepared according to Reaction Scheme III, wherein n is as defined above, R_d is alkyl, alkoxy, or $-N(R_9)_2$ and R_{2b} and R_{1-1b} are subsets of R_2 and R_{1-1} as defined above that do not include those substituents that one skilled in the art would recognize as being susceptible to reduction under the acidic hydrogenation conditions of the reaction. These susceptible groups include, for example, alkenyl, alkynyl, and aryl groups and groups bearing nitro substituents.

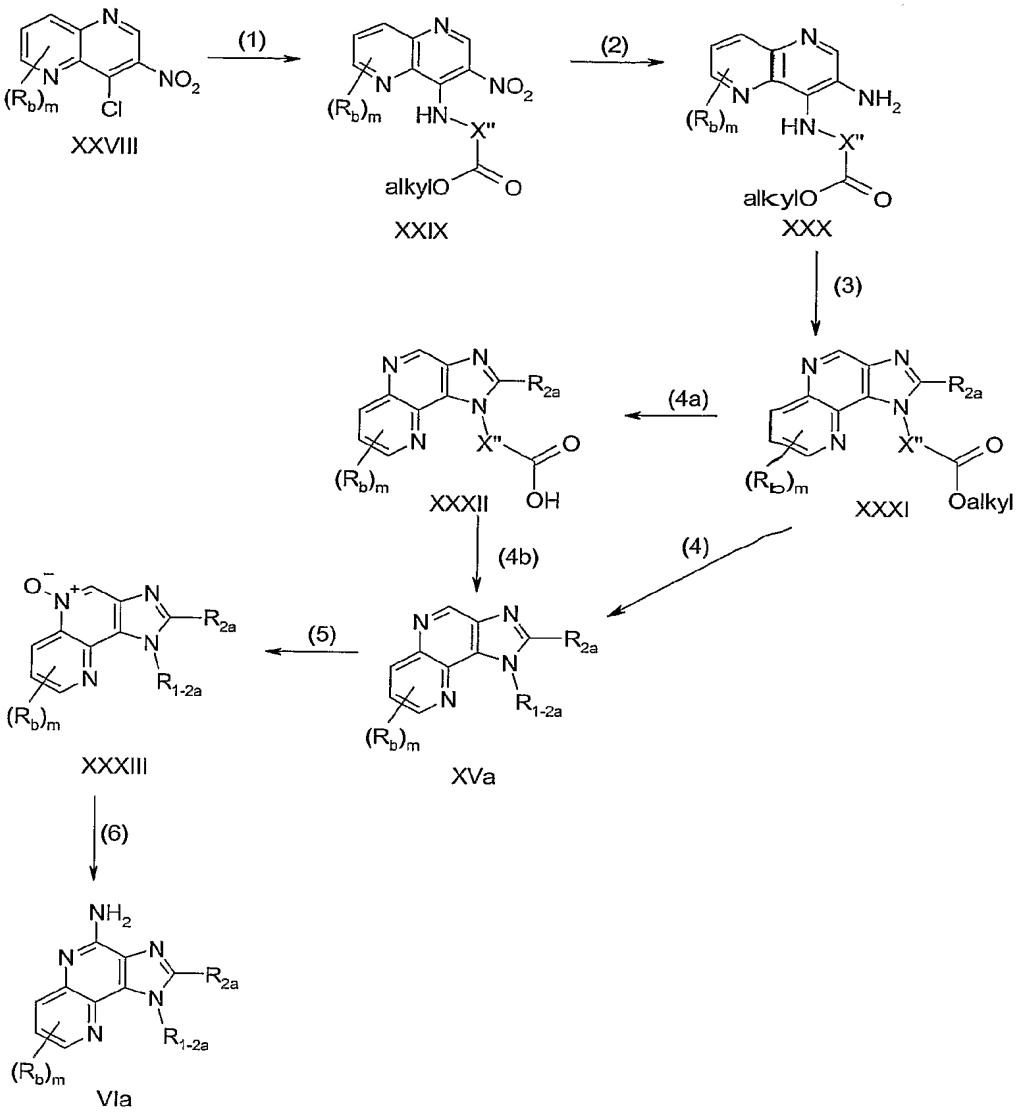
As shown in Reaction Scheme III, an 1*H*-imidazo[4,5-*c*]quinoline of Formula IVc can be reduced to a 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula Vb, a subgenus of Formulas I, II, and V. The reaction is conveniently carried out under hetereogeneous hydrogenation conditions by adding platinum (IV) oxide to a solution of the compound of Formula IVc in trifluoroacetic acid and placing the reaction under hydrogen pressure. The reaction can be carried out on a Parr apparatus at ambient temperature. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Reaction Scheme III



Compounds of the invention can be prepared according to Reaction Scheme IV, wherein R_b, X", R_{2a} and m are as defined above and R_{1-2a} is a subset of R_{1-2} as defined above that does not include those substituents that one skilled in the art would recognize as being susceptible to oxidation in step (5). These substituents include -S- and heteroaryl groups. Reaction Scheme IV begins with a 4-chloro-3-nitro[1,5]naphthyridine of Formula XXVIII. Compounds of Formula XXVIII and their preparation are known; see, for example, U.S. Patents Nos. 6,194,425 (Gerster) and 6,518,280 (Gerster). Steps (1) through (6) of Reaction Scheme IV can be carried out as described for the corresponding steps (1) through (6) of Reaction Scheme I to provide an amide-substituted 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula VIa, a subgenus of Formulas I, II, and VI. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Reaction Scheme IV



For some embodiments, compounds of the invention are prepared according to Reaction Scheme V, where $R_{1\text{-}1}$, R_2, R_{A1}, R_{B1}, and X_a are as defined above and Ph is phenyl. In step (1) of Reaction Scheme V, a 2,4-dichloro-3-nitropyridine of Formula XXXIV is reacted with an amino ester of the Formula $H_2N\text{-}X_a\text{-}C(O)\text{-}O\text{-alkyl}$ or a hydrochloride salt thereof to form a 2-chloro-3-nitropyridine of Formula XXXV. The reaction is conveniently carried out by combining an amino ester of Formula $H_2N\text{-}X_a\text{-}C(O)\text{-}O\text{-alkyl}$ - HCl and a 2,4-dichloro-3-nitropyridine of Formula XXXIV in the presence

of a base such as triethylamine in an inert solvent such as *N*,*N*-dimethylformamide (DMF). The reaction can be carried out at ambient temperature, and the product can be isolated from the reaction mixture using conventional methods. Many 2,4-dichloro-3-nitropyridines of the Formula XXXIV are known and can be readily prepared using known synthetic methods. (See, for example, Dellaria et al, U.S. Pat. No. 6,525,064 and the references cited therein.)

In step (2) of Reaction Scheme V a 2-chloro-3-nitropyridine of Formula XXXV is reacted with an alkali metal azide to provide an 8-nitrotetrazolo[1,5-*a*]pyridin-7-amine of Formula XXXVI. The reaction can be carried out by combining the compound of Formula XXXV with an alkali metal azide, for example, sodium azide, in a suitable solvent such as acetonitrile/water, preferably 90/10 acetonitrile/water, in the presence of cerium III chloride, preferably cerium III chloride heptahydrate. Optionally, the reaction can be carried out with heating, for example, at the reflux temperature. Alternatively, the reaction can be carried out by combining the compound of Formula XXXV with an alkali metal azide, for example, sodium azide, in a suitable solvent such as DMF and heating, for example to about 50-60 °C, optionally in the presence of ammonium chloride. The product can be isolated from the reaction mixture using conventional methods.

In step (3) of Reaction Scheme V, an 8-nitrotetrazolo[1,5-*a*]pyridin-7-amine of Formula XXXVI is reduced to provide a tetrazolo[1,5-*a*]pyridine-7,8-diamine of Formula XXXVII. The reduction can be carried out by hydrogenation using a conventional heterogeneous hydrogenation catalyst, for example, platinum on carbon or palladium on carbon. The reaction can conveniently be carried out on a Parr apparatus in a suitable solvent such as acetonitrile or ethyl acetate. The product can be isolated from the reaction mixture using conventional methods. Alternatively, the reduction can be carried out using the one- to two-phase sodium dithionite reduction described in step (2) of Reaction Scheme I.

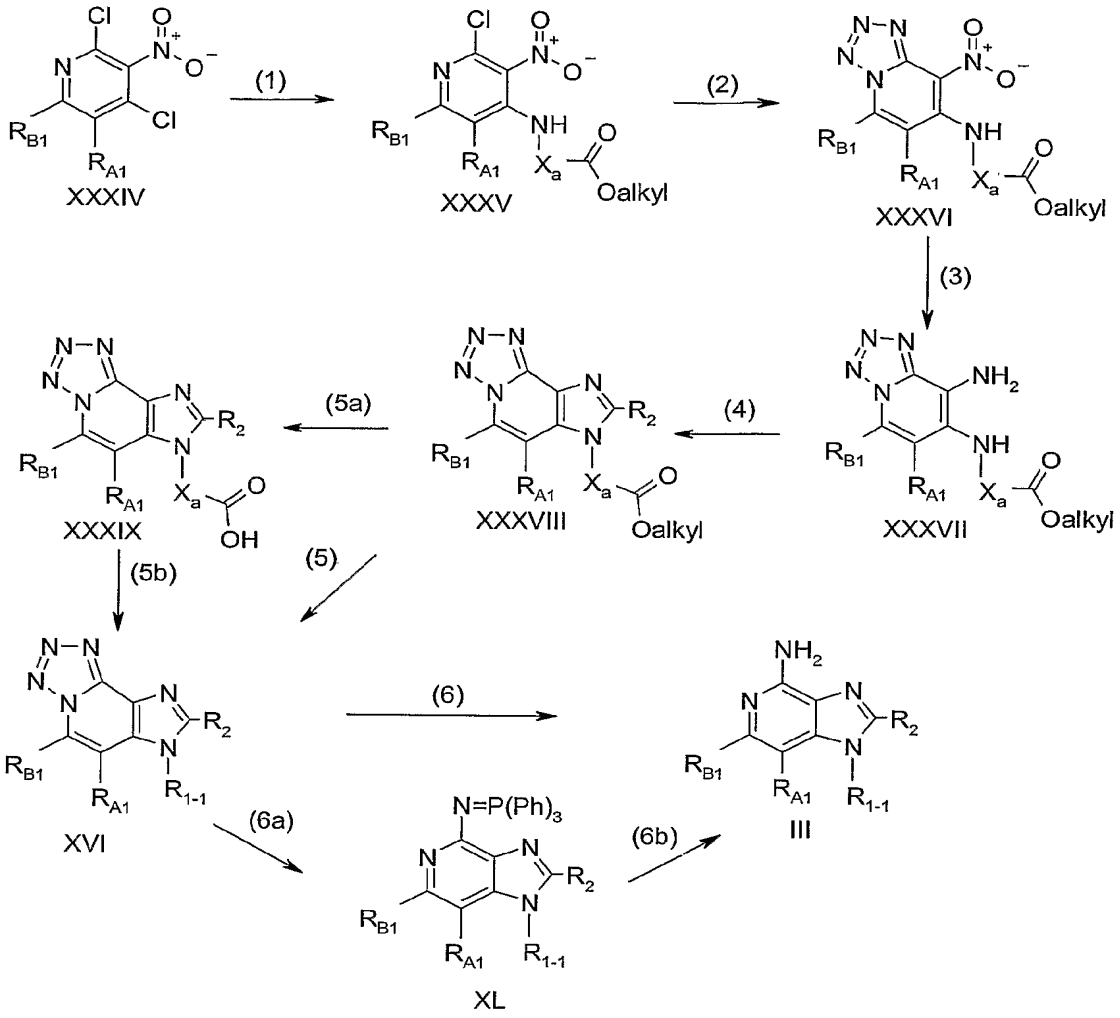
In step (4) of Reaction Scheme V, a tetrazolo[1,5-*a*]pyridine-7,8-diamine of Formula XXXVII is reacted with a carboxylic acid or equivalent thereof to provide a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula XXXVIII. The reaction can be carried out as described in step (3) of Reaction Scheme I, and the product can be isolated from the reaction mixture using conventional methods.

In step (5) or steps (5a) and (5b) of Reaction Scheme V, the ester group of a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula XXXVIII is converted to an amide to provide an amide-substituted 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula XXVI. The reaction can be carried out as described in step (4) or steps (4a) and (4b) of Reaction Scheme I, and the product can be isolated by conventional methods.

In step (6) of Reaction Scheme V, the tetrazolo ring is reductively removed from a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula XVI to provide an amide-substituted 1*H*-imidazo[4,5-*c*]pyridin-4-amine of Formula III or a pharmaceutically acceptable salt thereof. The reaction can be carried out by reacting the 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula XVI with hydrogen in the presence of a catalyst and an acid. The hydrogenation can be conveniently run at ambient temperature on a Parr apparatus with a suitable catalyst, such as platinum IV oxide, and a suitable acid, such as trifluoroacetic acid. The product or pharmaceutically acceptable salt thereof can be isolated from the reaction mixture using conventional methods.

Alternatively, the tetrazolo ring can be removed from a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula XVI as shown in step (6a) by reaction with triphenylphosphine to form an *N*-triphenylphosphinyl intermediate of Formula XL. The reaction with triphenylphosphine can be run in a suitable solvent such as toluene or 1,2-dichlorobenzene under an atmosphere of nitrogen with heating, for example at the reflux temperature. In step (6b) of Reaction Scheme V an *N*-triphenylphosphinyl intermediate of Formula XL is hydrolyzed to provide an amide-substituted 1*H*-imidazo[4,5-*c*]pyridin-4-amine of Formula III. The hydrolysis can be carried out by general methods well known to those skilled in the art, for example, by heating in a lower alkanol in the presence of an acid. The product can be isolated from the reaction mixture using conventional methods as the compound of Formula III or as a pharmaceutically acceptable salt thereof.

Reaction Scheme V

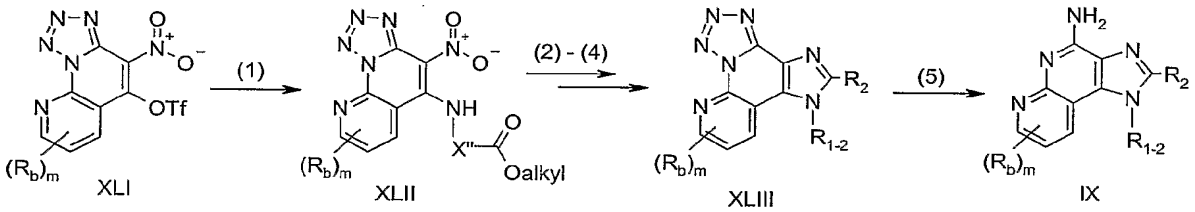


For some embodiments, naphthyridines of the invention are prepared from tetrazolo compounds of Formulas XLI and XLIV according to Reaction Scheme VI and Reaction Scheme VII, wherein $R_{1\text{-}2}$, R_2, R_b, m, and X" are as defined above and -OTf is a trifluoromethanesulfonate group. Compounds of Formula XLI and XLIV and synthetic routes to these compounds are known; see, for example, U.S. Patent Nos. 6,194,425 (Gerster) and 6,518,280 (Gerster).

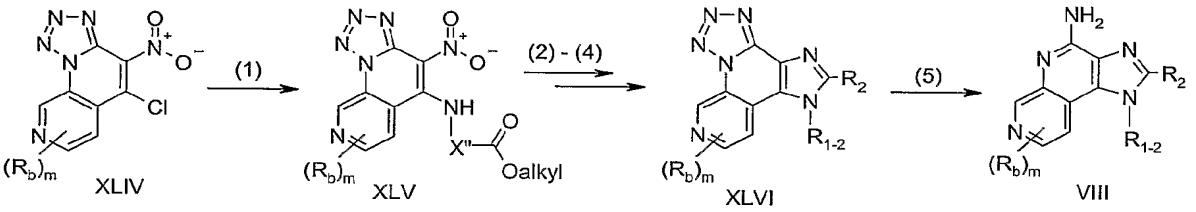
In step (1) of Reaction Scheme VI or VII, a tetrazolonaphthyridine of Formula XLI or XLIV is reacted with an amino ester of the Formula H_2N-X"-C(O)-O-alkyl or a hydrochloride salt thereof to form a compound of Formula XLII or XLV. The reaction

can be carried out as described in step (1) of Reaction Scheme I. An ester-substituted tetrazolonaphthyridine of Formula XLII or XLV is converted in steps (2) through (4) of Reaction Scheme VI or VII to a compound of Formula XLIII or XLVI according to the methods of steps (2), (3), and (4) or (4a) and (4b) of Reaction Scheme I. The tetrazolo group of a compound of Formula XLIII or XLVI can then be removed to provide a 1*H*-imidazo[4,5-*c*]naphthyridin-4-amine of Formula IX or VIII, which are subgenera of Formulas I and II. The removal of the tetrazolo group can be carried out as described in step (6) or steps (6a) and (6b) of Reaction Scheme V or by methods described in U.S. Patent Nos. 6,194,425 (Gerster) and 6,518,280 (Gerster). The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Reaction Scheme VI



Reaction Scheme VII



Compounds of the invention can be prepared according to Reaction Scheme VIII wherein R_a, R_{1-1}, R_{2a}, and n are as defined above. In step (1) of Reaction Scheme VIII, a 4-chloro-3-nitroquinoline of Formula XX is reduced to provide a 3-amino-4-chloroquinoline of Formula XLVII. The reduction can be carried out using one of the methods described in step (2) of Reaction Scheme I, and the product of Formula XLVII or a salt thereof can be isolated by conventional methods. Some compounds of Formula XLVII are known. For example, 3-amino-4-chloroquinoline, 3-amino-4,5-dichloroquinoline, and 3-amino-4,7-dichloroquinoline have been prepared by Surrey et al.,

Journal of the American Chemical Society, 73, pp. 2413-2416 (1951). Compounds of Formula XLVII can also be prepared from 3-nitroquinolin-4-ols by the reduction described above followed by chlorination using conventional methods.

In step (2) of Reaction Scheme VIII, a 3-amino-4-chloroquinoline of Formula XLVII is reacted with an acid halide of Formula $R_{2a}C(O)Cl$ or $R_{2a}C(O)Br$ to provide an *N*-(4-chloroquinolin-3-yl) amide of Formula XLVIII. The acid halide is conveniently added to a solution of a compound of Formula XLVII in a suitable solvent such as anhydrous dichloromethane in the presence of a base such as triethylamine. The reaction can be run at a reduced temperature, for example, 0° C, or at ambient temperature. For compounds wherein R_{2a} is hydrogen, the compound of Formula XLVII can be reacted with a formylating agent such as, for example, diethoxymethyl acetate. The product can be isolated by conventional methods.

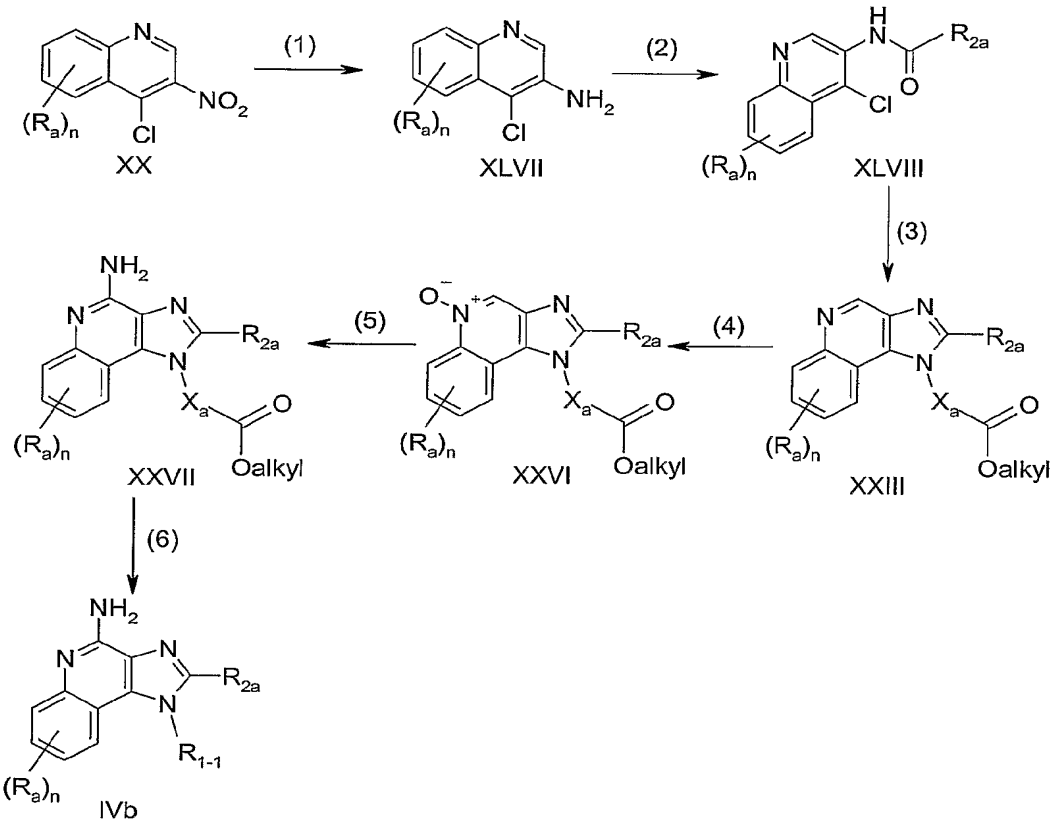
In step (3) of Reaction Scheme VIII, an *N*-(4-chloroquinolin-3-yl) amide of Formula XLVIII is reacted with an amino ester of the Formula H_2N-X_a-C(O)-O-alkyl or a hydrochloride salt thereof to displace the chloro group, and the resulting intermediate is cyclized to form a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXIII. The chloride displacement is conveniently carried out by combining a compound of Formula XLVIII with an amino ester of Formula H_2N-X_a-C(O)-O-alkyl. The reaction may be carried out neat at an elevated temperature such as the temperature required to melt the mixture. The reaction may also be carried out in an alcoholic solvent at the reflux temperature of the solvent. The product can be isolated and optionally purified using conventional techniques before it is heated and cyclized to provide a compound of Formula XXIII. The cyclization reaction is conveniently carried out in a solvent such as toluene, optionally in the presence of a catalyst such as pyridine hydrochloride or pyridinium *p*-toluenesulfonate. The cyclization may be carried out at an elevated temperature, such as the reflux temperature of the solvent. The 1*H*-imidazo[4,5-*c*]quinoline of Formula XXIII can be isolated using conventional methods. Glycine ethyl ester hydrochloride can be employed as the amino ester in this step to provide a compound wherein X_a is $-CH_2-$.

In step (4) of Reaction Scheme VIII, an ester-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XXIII is oxidized to an *N*-oxide of Formula XXVI, which is then aminated in step (5) to provide an ester-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine

Formula XXVII. Steps (4) and (5) of Reaction Scheme VIII can be carried out as described for steps (5) and (6) of Reaction Scheme I.

In step (6) of Reaction Scheme VIII, an ester-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine Formula XXVII is heated in the presence of an amine or ammonium acetate according to one of the methods described in step (3) of Reaction Scheme II to provide a compound of Formula IVb. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

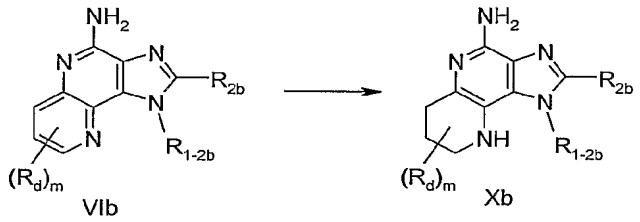
Reaction Scheme VIII



Compounds of the invention can also be prepared according to Reaction Scheme IX, wherein R_{2b}, R_d, and m are as defined above, and $R_{1\text{-}2b}$ is a subset of $R_{1\text{-}2}$ as defined above that does not include those substituents that one skilled in the art would recognize as being susceptible to reduction under the acidic hydrogenation conditions of the reaction. These susceptible groups include, for example, alkenyl, alkynyl, and aryl groups and groups bearing nitro substituents.

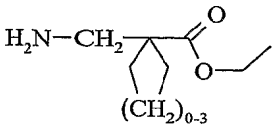
In Reaction Scheme IX, a 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula VIb is reduced to a 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula Xb, a subgenus of Formulas I, II, and X. The reaction is conveniently carried out using the conditions described in Reaction Scheme III, and the product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Reaction Scheme IX



Compounds of the Formula H_2N-X_a-C(O)-O-alkyl or H_2N-X"-C(O)-O-alkyl in which X_a or X" contains a cyclic alkyl group can be used in step (1) of Reaction Scheme I, IV, V, VI, or VII or in step (3) of Reaction Scheme VIII to prepare some compounds of the invention. These amino esters can be readily prepared in two steps from ethylcyanoacetate. In the first step, ethylcyanoacetate is combined with an alkyl dihalide, for example a dibromide of formula Br-alkylene-Br, in the presence of a base such as potassium carbonate in a suitable solvent such as acetone or DMF. The reaction can be carried out at ambient temperature or at an elevated temperature, and the product can be isolated by conventional methods. Numerous dibromides of formula Br-alkylene-Br can be obtained commercially, including, for example, 1,2-dibromoethane, 1,3-dibromopropane, 1,4-dibromobutane, and 1,5-dibromopentane. The resulting 1-cyanocycloalkanecarboxylate is then reduced to a 1-aminomethylcycloalkanecarboxylate using heterogeneous hydrogenation conditions. The reduction is conveniently carried out in the presence of acid, for example concentrated hydrochloric acid, with catalytic platinum (IV) oxide in a suitable solvent such as ethanol. The hydrogenation is conveniently carried out in a Parr apparatus, and the product can be isolated by conventional methods. When 1,2-dibromoethane, 1,3-dibromopropane, 1,4-

dibromobutane, or 1,5-dibromopentane is used in the first step of this method, an amino

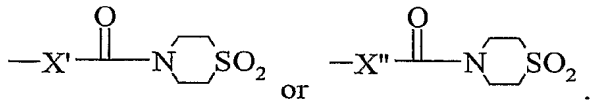


ester of formula is obtained.

Synthetic transformations can be made at the R_2 position in many of the compounds shown in Reaction Schemes I through IX, if, for example, the carboxylic acid or equivalent thereof used in step (3) of Reaction Scheme I, IV, VI, or VII, step (4) of Reaction Scheme V, or step (2) of Reaction Scheme VIII contains a protected hydroxy or amino group. Some acid chlorides of this type are commercially available; others can be prepared by known synthetic methods. A protected hydroxy or amino group thus installed at the R_2 position can then be deprotected by a variety of methods well known to one of skill in the art. For example, hydroxyalkylenyl group is conveniently introduced at the R_2 position by the demethylation of a methoxyalkylenyl group, which can be installed by using a methoxy-substituted carboxylic acid equivalent, for example, methoxyacetyl chloride and 2-methoxypropionyl chloride, in step (3) of Reaction Scheme I. The demethylation can be carried out by treating a compound wherein R_2 is a methoxyalkylenyl group with boron tribromide in a suitable solvent such as dichloromethane at a sub-ambient temperature such as 0 °C. The resulting hydroxy group may then be oxidized to an aldehyde or carboxylic acid or converted to a leaving group such as, for example, a chloro group using thionyl chloride or a trifluoromethanesulfonate group using trifluoromethanesulfonic anhydride. The resulting leaving group can then be displaced by a variety of nucleophiles. Sodium azide can be used as the nucleophile to install an azide group, which can then be reduced to an amino group using heterogeneous hydrogenation conditions. An amino group at the R_2 position can be converted to an amide, sulfonamide, sulfamide, or urea using conventional methods. A leaving group at R_2, such as a chloro or trifluoromethanesulfonate group, can also be displaced with a secondary amine, a substituted phenol, or a mercaptan in the presence of a base such as potassium carbonate. For examples of these and other methods used to install a variety of groups at the R_2 position, see U.S. Patent No. 5,389,640 (Gerster et al.).

Some further synthetic elaborations can also be carried out at the R_{1-1} or R_{1-2} group in compounds prepared in Reaction Schemes I through IX. For example, the cyclic amine group added in step (4) or (4b) in Reaction Scheme I or IV may be thiomorpholine, which

can be oxidized to a 1,1-dioxothiomorpholine group in step (5) of Reaction Scheme I or IV using an excess of the oxidizing agent. Step (6) of Reaction Scheme I or IV may then be carried out to provide a compound of Formula IVa or VIa, wherein R_{1-1} or R_{1-2} is



The amination reaction shown in step (6) of Reaction Scheme I or IV, step (2) of Reaction Scheme II, or step (5) of Reaction Scheme VIII can be carried out by an alternative to the method described in step (6) of Reaction Scheme I. The reaction can be carried out by treating a 5*N*-oxide of Formula XXV, XXVI, or XXXIII with trichloroacetyl isocyanate followed by hydrolysis of the resulting intermediate to provide a compound of Formula IVa, XXVII, or VIa, respectively. The reaction is conveniently carried out in two steps by (i) adding trichloroacetyl isocyanate to a solution of a 5*N*-oxide in a solvent such as dichloromethane and stirring at ambient temperature to provide an isolable amide intermediate. In step (ii), a solution of the intermediate in methanol is treated with a base such as sodium methoxide or ammonium hydroxide at ambient temperature. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Compounds of the invention can also be prepared using variations of the synthetic routes shown in Reaction Schemes I through IX that would be apparent to one of skill in the art. For example, the synthetic route shown in Reaction Scheme VIII for the preparation of 1*H*-imidazo[4,5-*c*]quinolines can be used to prepare 1*H*-imidazo[4,5-*c*][1,5]naphthyridines by starting with a 4-chloro-3-nitro[1,5]naphthyridine of Formula XXVIII in lieu of the 4-chloro-3-nitroquinoline of Formula XX. Compounds of the invention can also be prepared using the synthetic routes described in the EXAMPLES below.

Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound or salt of the invention as described above in combination with a pharmaceutically acceptable carrier.

The terms "a therapeutically effective amount" and "effective amount" mean an amount of the compound or salt sufficient to induce a therapeutic or prophylactic effect,

such as, for example, cytokine induction, immunomodulation, antitumor activity, and/or antiviral activity. Although the exact amount of active compound or salt used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art such as, for example, the physical and chemical nature of the compound or salt, the nature of the carrier, and the intended dosing regimen, it is anticipated that the compositions of the invention will contain sufficient active ingredient to provide a dose of about 100 nanograms per kilogram (ng/kg) to about 50 milligrams per kilogram (mg/kg), preferably about 10 micrograms per kilogram (μg/kg) to about 5 mg/kg, of the compound or salt to the subject. A variety of dosage forms may be used, such as tablets, lozenges, capsules, parenteral formulations, syrups, creams, ointments, gels, aerosol formulations, transdermal patches, transmucosal patches and the like.

The compounds or salts of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds or salts of the invention may be administered in combination with one another or with other active agents, including, for example, additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

Compounds or salts of the invention have been shown to induce the production of certain cytokines in experiments performed according to the test set forth below. These results indicate that the compounds or salts are useful as immune response modifiers that can modulate the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of compounds or salts of the invention generally include interferon-α (IFN-α) and/or tumor necrosis factor-α (TNF-α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds or salts of the invention include IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds or salts useful in the treatment of viral diseases and neoplastic diseases. Accordingly, one aspect of the invention provides a method of inducing cytokine biosynthesis in an animal. Generally, the method includes administering an effective amount of a compound or salt or composition of the invention to the animal. The animal to which the compound or salt or composition is administered for induction of cytokine biosynthesis may have a disease

as described *infra*, for example a viral disease or a neoplastic disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

In addition to the ability to induce the production of cytokines, compounds or salts of the invention can affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds or salts may also activate macrophages, which in turn stimulate secretion of nitric oxide and the production of additional cytokines. Further, the compounds or salts may cause proliferation and differentiation of B-lymphocytes.

Compounds or salts of the invention can also have an effect on the acquired immune response. For example, the production of the T helper type 1 (T_H1) cytokine IFN-γ may be induced indirectly and the production of the T helper type 2 (T_H2) cytokines IL-4, IL-5 and IL-13 may be inhibited upon administration of the compounds or salts.

Whether for prophylaxis or therapeutic treatment of a disease, and whether for effecting innate or acquired immunity, the compound or salt or composition may be administered alone or in combination with one or more active components as in, for example, a vaccine adjuvant. When administered with other components, the compound or salt and other component or components may be administered separately; together but independently such as in a solution; or together and associated with one another such as (a) covalently linked or (b) non-covalently associated, e.g., in a colloidal suspension.

Conditions for which compounds or salts identified herein may be used as treatments include, but are not limited to:

(a) viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus (e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenzavirus), a paramyxovirus (e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV)), a coronavirus (e.g., SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV);

(b) bacterial diseases such as, for example, diseases resulting from infection by bacteria of, for example, the genus Escherichia, Enterobacter, Salmonella, Staphylococcus, Shigella, Listeria, Aerobacter, Helicobacter, Klebsiella, Proteus, Pseudomonas, Streptococcus, Chlamydia, Mycoplasma, Pneumococcus, Neisseria, Clostridium, Bacillus, Corynebacterium, Mycobacterium, Campylobacter, Vibrio, Serratia, Providencia, Chromobacterium, Brucella, Yersinia, Haemophilus, or Bordetella;

(c) other infectious diseases, such chlamydia, fungal diseases including but not limited to candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis, or parasitic diseases including but not limited to malaria, pneumocystis carnii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection;

(d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, renal cell carcinoma, Kaposi's sarcoma, melanoma, leukemias including but not limited to myelogeous leukemia, chronic lymphocytic leukemia, multiple myeloma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, B-cell lymphoma, and hairy cell leukemia, and other cancers;

(e) T_H2-mediated, atopic diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, and Ommen's syndrome;

(f) certain autoimmune diseases such as systemic lupus erythematosus, essential thrombocythaemia, multiple sclerosis, discoid lupus, alopecia areata; and

(g) diseases associated with wound repair such as, for example, inhibition of keloid formation and other types of scarring (e.g., enhancing wound healing, including chronic wounds).

Additionally, compounds or salts of the present invention may be useful as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such as, for example, live viral, bacterial, or parasitic immunogens; inactivated viral, tumor-derived, protozoal, organism-derived, fungal, or bacterial immunogens, toxoids; toxins; self-antigens; polysaccharides; proteins; glycoproteins; peptides; cellular vaccines; DNA vaccines; autologous vaccines; recombinant proteins; and the like, for use in connection with, for example, BCG, cholera, plague, typhoid, hepatitis A, hepatitis B, hepatitis C, influenza A, influenza B, parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria, hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines,

adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, yellow fever, and Alzheimer's Disease.

Compounds or salts of the present invention may be particularly helpful in individuals having compromised immune function. For example, compounds or salts may be used for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need thereof (having the disease) by administering a therapeutically effective amount of a compound or salt of the invention to the animal.

An amount of a compound or salt effective to induce cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12 that is increased (induced) over a background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. The invention also provides a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. An amount of a compound or salt effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg.

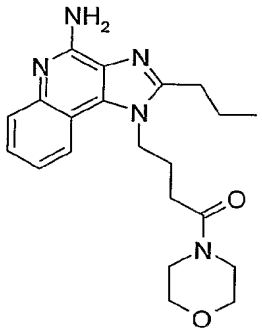
In addition to the formulations and uses described specifically herein, other formulations, uses, and administration devices suitable for compounds of the present invention are described in, for example, International Publication Nos. WO 03/077944 and WO 02/036592, U.S. Patent No. 6,245,776, and U.S. Publication Nos. 2003/0139364, 2003/185835, 2004/0258698, 2004/0265351, 2004/076633, and 2005/0009858.

EXAMPLES

Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

Example 1

1-(4-Morpholin-4-yl-4-oxobutyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

Ethanol (500 mL) was cooled to 0 °C, and thionyl chloride (85 mL, 1.2 mol) was added dropwise with stirring. The reaction was stirred for one hour at 0 °C, and solid 4-aminobutyric acid (100 g, 0.97 mol) was then added. After ten minutes of stirring, the reaction was allowed to warm to ambient temperature and stirred for two hours. The reaction was then allowed to stand at ambient temperature overnight. The ethanol was removed under reduced pressure, and the solid residue was dissolved in ethyl acetate. After one hour, the solution was cooled to 0 °C, and a precipitate formed. The precipitate was isolated by filtration and washed with diethyl ether (300 mL) to provide 126.6 g of ethyl 4-aminobutyrate hydrochloride as a white solid. A precipitate formed in the filtrate and was isolated by filtration to provide 19.1 g of ethyl 4-aminobutyrate hydrochloride as a white solid.

Part B

Triethylamine (50.0 mL, 358 mmol) and potassium carbonate (40 g, 290 mmol) were added to a solution of 4-chloro-3-nitroquinoline (49.6 g, 238 mmol) in tetrahydrofuran (THF) (100 mL) and chloroform (250 mL). Ethyl 4-aminobutyrate hydrochloride (43.8 g, 262 mmol) was added in portions over a period of five minutes during which time an ice bath was used to cool the reaction. The reaction was stirred with cooling for 30 minutes, allowed to warm to ambient temperature, and stirred overnight. An analysis by thin layer chromatography (TLC) indicated the presence of 4-chloro-3-nitroquinoline. Additional ethyl 4-aminobutyrate hydrochloride (8.0 g, 48 mmol) was added, and the reaction was stirred at ambient temperature for one hour and then heated at reflux for two hours. Additional triethylamine (20 mL) was added, and the reaction was heated at reflux for one hour, cooled to ambient temperature, washed with water (3 x 100 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide 63.8 g of ethyl 4-(3-nitroquinolin-4-ylamino)butyrate as a yellow solid.

Part C

A mixture of ethyl 4-(3-nitroquinolin-4-ylamino)butyrate (20.0 g, 65.9 mmol), 10% palladium on carbon (0.50 g), and ethanol (250 mL) was added to a Parr vessel, and the reaction was placed under hydrogen pressure (43 psi, 3.0 x 10^5 Pa) for 3.5 hours. The pressure decreased to 31 psi (2.1 x 10^5 Pa) during the reaction. The reaction mixture was filtered through a layer of CELITE filter agent, and the filtrate was concentrated under reduced pressure.

Part D

Trimethyl orthobutyrate (10.4 g, 70.2 mmol) and pyridinium *p*-toluenesulfonate (0.25 g, 1.0 mmol) were added to a solution of the material from Part C in toluene (350 mL), and the reaction was heated at reflux under a Dean-Stark trap for three hours while the distillate was periodically removed. The toluene was removed under reduced pressure, and the residue was stirred with 70:30 hexanes:ethyl acetate (75 mL). Additional hexane (50 mL) was added to form a precipitate. The supernatant liquid was decanted away to afford 6.75 g of a brown solid, which was mixed with 20.8 g of material from another run. The crude product was then purified by column chromatography on silica gel (eluting with 95:5 dichloromethane:methanol) to provide 14.2 g of ethyl 4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butanoate as an oil that crystallized upon standing.

Part E

Trimethylaluminum (available as a 2 M solution in toluene, 15.5 mL, 31.0 mmol) was added dropwise with stirring to a solution of morpholine (2.7 mL, 31 mmol) in dichloromethane (75 mL) at ambient temperature. After 20 minutes, a solution of ethyl 4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butanoate (5.0 g, 15 mmol) in dichloromethane (15 mL) was added dropwise. The reaction was then heated at reflux for three days. An analysis by high-performance liquid chromatography (HPLC) indicated the presence of starting material, and additional morpholine (0.2 mL) was added. The reaction was heated at reflux for three hours and then allowed to stand at room temperature over three days. Hydrochloric acid (4 mL of 10%) was slowly added followed by saturated aqueous sodium bicarbonate (8 mL). The organic layer was decanted away from solids formed during the reaction. The solids were extracted with dichloromethane (2 x 50 mL), and the combined organic fractions were washed with 5% aqueous sodium hydroxide (35 mL) and saturated aqueous sodium bicarbonate (35 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide a light yellow solid.

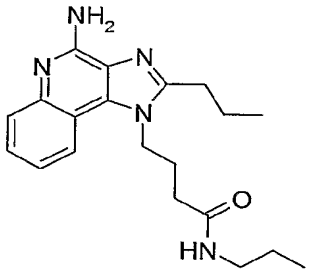
Part F

3-Chloroperoxybenzoic acid (mCPBA) (available as 77% pure material, 8.5 g, 38 mmol) was added in portions over a period of two minutes to a solution of the material from Part E in dichloromethane (100 mL), and the reaction was stirred for 45 minutes at ambient temperature and then washed with 5% aqueous sodium hydroxide (2 x 35 mL) and water (25 mL). Concentrated ammonium hydroxide (100 mL of 29%) and *p*-toluenesulfonyl chloride (4.9 g, 26 mmol) were then sequentially added with vigorous stirring, and the reaction was stirred for 30 minutes. The aqueous layer was separated and extracted with dichloromethane (4 x 50 mL). The combined organic fractions were washed with 5% aqueous sodium hydroxide solution (2 x 50 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure. The residue was recrystallized twice from acetonitrile (15 mL) and methanol (4 mL) to provide 0.96 g of a light orange solid. A portion was dried overnight in a vacuum oven to provide 1-(4-morpholin-4-yl-4-oxobutyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a light yellow needles, mp 200-202 °C.

Anal. Calcd for $C_{21}H_{27}N_5O_2$: C, 66.12; H, 7.13; N, 18.36. Found: C, 65.86; H, 7.39; N, 18.21.

Example 2

4-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylbutanamide



Part A

A solution of *n*-propylamine (3.0 mL, 36 mmol) in dichloromethane (75 mL) was cooled to 0 °C; trimethylaluminum (available as a 2 M solution in toluene, 18 mL, 36 mmol) was added dropwise with stirring over a period of three minutes. The reaction was stirred for one hour at 0 °C and 30 minutes at ambient temperature. A solution of ethyl 4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butanoate (5.80 g, 17.8 mmol, prepared as described in Parts A-D of Example 1) in dichloromethane (30 mL) was added, and the reaction was then heated at reflux for three days. The work-up procedure described in Part E of Example 1 was followed to provide *N*-propyl-4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butanamide as a brown oil.

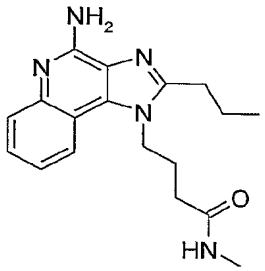
Part B

N-Propyl-4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butanamide (5.6 g, 15 mmol) was treated with mCPBA (8.5 g, 38 mmol), concentrated ammonium hydroxide (100 mL), and *p*-toluenesulfonyl chloride (4.9 g, 26 mmol) according to the method described in Part F of Example 1. The crude product was dissolved in hot toluene (25 mL) and dichloromethane. A precipitate slowly formed, was isolated by filtration, and was washed with toluene (15 mL). The solid was recrystallized twice from 4:1 methanol:water (25 mL), and the crystals were heated at reflux in chloroform in the presence of charcoal (1 g). The mixture was filtered through a layer of CELITE filter agent, and the filtrate was concentrated under reduced pressure. The residue was recrystallized twice from methanol:water and twice from toluene (15 mL) and dried overnight in a vacuum oven to provide 0.74 g of 4-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylbutanamide as a grey solid, mp 161-163 °C.

Anal. Calcd for $C_{20}H_{27}N_5O$: C, 67.96; H, 7.70; N, 19.81. Found: C, 67.64; H, 7.92; N, 19.83.

Example 3

4-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methylbutanamide



Part A

A suspension of 4-chloro-3-nitroquinoline (75.0 g, 0.360 mol) in chloroform (400 mL) was cooled to 0 °C; triethylamine (75 mL, 0.54 mol) was added. Ethyl 4-aminobutyrate hydrochloride (66.0 g, 0.390 mol), prepared as described in Part A of Example 1, was added in portions over a period of five minutes. The reaction was stirred at 0 °C for 1 hour, allowed to warm to ambient temperature, and stirred overnight. An analysis by thin layer chromatography (TLC) indicated the presence of 4-chloro-3-nitroquinoline. Additional triethylamine (15 mL) was added, and the reaction was stirred for one hour. Additional ethyl 4-aminobutyrate hydrochloride (10.0 g) was added, and the reaction was heated at reflux for five hours. Additional triethylamine (22 mL) was added, and the reaction was stirred overnight at ambient temperature and heated at reflux for one hour. An analysis by TLC indicated the reaction was complete. The reaction was cooled to ambient temperature and washed with water (5 x 400 mL), and the resulting solution was used in Part B.

Part B

Chloroform was added to the material from Part A to provide a volume of 750 mL. Water (600 mL), potassium carbonate (80 g, 0.6 mol), and 1,1'-di-*n*-octyl-4,4'-bipyridinium dibromide (0.50 g, 0.92 mmol) were added. Sodium hydrosulfite (available as 85% pure material, 120 g, 0.68 mol) was then added in portions over a period of one hour, and the reaction was stirred at ambient temperature for three days. The reaction was not complete as evidenced by an HPLC analysis. Additional sodium hydrosulfite (20 g), potassium carbonate (20 g), and 1,1'-di-*n*-octyl-4,4'-bipyridinium dibromide (0.25 g) were

added, and the reaction was stirred for three hours. Additional sodium hydrosulfite (20 g), potassium carbonate (20 g), and water (200 mL) were added, and the reaction was stirred overnight. Additional sodium hydrosulfite (5 g) and potassium carbonate (5 g) were added, and the reaction was stirred for three hours. Additional sodium hydrosulfite (5 g) was added, and the reaction was stirred for two hours. An analysis by TLC indicated the reaction was complete. The organic layer was separated and washed with water (5 x 200 mL), dried over potassium carbonate, and concentrated under reduced pressure to provide 97.4 g of ethyl 4-[(3-aminoquinolin-4-yl)amino]butanoate as a dark oil.

Part C

A solution of ethyl 4-[(3-aminoquinolin-4-yl)amino]butanoate (72.0 g, 263 mmol) in toluene (700 mL) was heated at reflux for 10 minutes and then cooled slightly. Trimethyl orthobutyrate (42 g, 280 mmol) and pyridinium *p*-toluenesulfonate (1.0 g, 4.0 mmol) were added, and the reaction was heated at reflux under a Dean-Stark trap for two hours while the distillate was periodically removed. The reaction was then stirred overnight at ambient temperature. Charcoal (5 g) was added, and the resulting mixture was heated at reflux for three hours and then filtered through a layer of CELITE filter agent. The filtrate was concentrated under reduced pressure to provide an oil that crystallized upon standing. The solid was dissolved in hot methanol (125 mL), and water (50 mL) was added. After one hour, the mixture was cooled in an ice bath to form a precipitate. The precipitate was isolated by filtration and dissolved in dichloromethane. A layer of water was present and was removed. The remaining solution was dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide 53.2 g of ethyl 4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butanoate.

Part D

A mixture of ethyl 4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butanoate (2.0 g, 6.1 mmol), THF (10 mL), and methylamine (available as a 40% solution in water, 4 mL, 52 mmol) was sealed in a high-pressure vessel and heated at 70 °C overnight. An analysis by TLC indicated the presence of starting material, and the reaction was sealed and heated at 80 °C for nine hours. The solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane (100 mL). The resulting solution was washed with 5% aqueous sodium hydroxide (2 x 25 mL), dried over potassium carbonate, filtered, and

concentrated under reduced pressure to provide 1.83 g of *N*-methyl-4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butanamide.

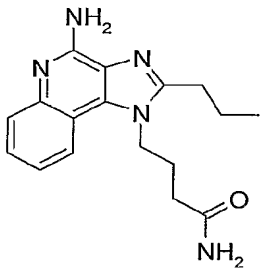
Part E

mCPBA (3.3 g, 15 mmol) was added to a solution of *N*-methyl-4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butanamide (1.83 g, 5.90 mmol) in chloroform (75 mL), and the reaction was stirred for 1.5 hours at ambient temperature. Concentrated ammonium hydroxide (75 mL of 29%) and *p*-toluenesulfonyl chloride (1.7 g, 8.9 mmol) were then sequentially added with stirring, and the reaction was stirred for 45 minutes. The aqueous layer was separated and extracted with chloroform (1 x 50 mL). The combined organic fractions were washed with 5% aqueous sodium hydroxide solution (2 x 50 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure. The residue was recrystallized from a mixture of toluene (20 mL) and methanol (4 mL) and then recrystallized three times from 5:1 methanol:water (18 mL) and dried overnight in a vacuum oven at 80 °C. During the recrystallization, the product was mixed with material from another run to provide 0.720 g of 4-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methylbutanamide as a tan solid, mp 177-179 °C.

Anal. Calcd for $C_{18}H_{23}N_5O \cdot 0.19\ H_2O$: C, 65.75; H, 7.17; N, 21.30. Found: C, 65.91; H, 7.35; N, 21.32.

Example 4

4-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butanamide



Part A

A solution of ethyl 4-[(3-aminoquinolin-4-yl)amino]butanoate (49.7 g, 182 mmol, prepared as described in Parts A and B of Example 3) in toluene (500 mL) was heated at reflux for 10 minutes and then cooled slightly. Trimethyl orthobutyrate (29.0 g, 197 mmol) and pyridinium *p*-toluenesulfonate (0.70 g, 2.8 mmol) were added, and the reaction

was heated at reflux under a Dean-Stark trap for 1.5 hours while the distillate was periodically removed. The reaction was allowed to stand overnight at ambient temperature. The toluene was removed under reduced pressure; chloroform (500 mL) and charcoal (4 g) were sequentially added. The resulting mixture was heated at reflux for one hour and then filtered through a layer of CELITE filter agent. The filtrate was washed with saturated aqueous sodium bicarbonate (100 mL), dried over potassium sulfate, filtered, and concentrated under reduced pressure to provide 49.4 g of ethyl 4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butanoate as a dark oil.

Part B

Concentrated ammonium hydroxide (8.0 mL of 29%) was added to a solution of ethyl 4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butanoate (5.1 g, 16 mmol) in 2-methyltetrahydrofuran (10 mL), and the mixture was heated overnight in a sealed high-pressure vessel at 80 °C. An analysis by liquid chromatography/mass spectrometry (LC/MS) indicated the reaction was incomplete. The solvents were evaporated under a stream of nitrogen, and ammonium acetate (10 g) was added. The vessel was sealed and heated overnight at 135 °C. The reaction was allowed to cool to ambient temperature, and water (50 mL) was added. The mixture was filtered, and the filtrate was washed with saturated aqueous sodium bicarbonate (25 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide 2.95 g of 4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butanamide as a light brown solid.

Part C

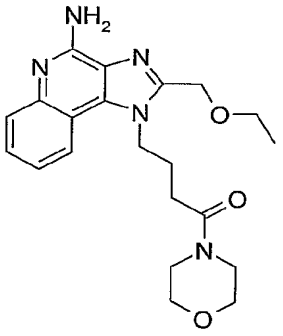
4-(2-Propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butanamide (2.90 g, 9.78 mmol) was treated with mCPBA (5.5 g, 25 mmol), concentrated ammonium hydroxide (100 mL of 29%), and *p*-toluenesulfonyl chloride (2.80 g, 14.7 mmol) according to the method described in Part E of Example 3. After the reaction solution was dried with potassium carbonate, it was decanted, and charcoal (2 g) was added. The mixture was heated at reflux for two hours, filtered through a layer of CELITE filter agent, and concentrated under reduced pressure. The crude solid was purified by column chromatography on silica gel (eluting with 90:10 dichloromethane:methanol) and combined with material from another run. The solid was recrystallized from 5:1 toluene:methanol (18 mL), dried overnight in a vacuum oven, recrystallized from ethanol:water, and dried overnight in a

vacuum oven to provide 4-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butanamide as a tan solid, mp 249-251 °C.

Anal. Calcd for $C_{17}H_{21}N_5O$: C, 65.57; H, 6.80; N, 22.49. Found: C, 65.24; H, 6.79; N, 22.16.

Example 5

2-(Ethoxymethyl)-1-(4-morpholin-4-yl-4-oxobutyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

A suspension of 4-chloro-3-nitroquinoline (40.0 g, 0.192 mol) in chloroform (250 mL) was cooled to 0 °C; triethylamine (75 mL, 0.54 mol) was added. Ethyl 4-aminobutyrate hydrochloride (35.0 g, 0.210 mol), prepared as described in Part A of Example 1, was added in portions over a period of two minutes. The reaction was stirred at 0 °C for 15 minutes, allowed to warm to ambient temperature, and stirred overnight. The reaction was heated at reflux for 15 minutes, and then chloroform (200 mL) was added. The resulting solution was washed with water (5 x 150 mL) and then used in Part B.

Part B

Water (400 mL), potassium carbonate (105 g, 0.760 mol), ethyl viologen dibromide (0.50 g, 1.3 mmol), and sodium hydrosulfite (115 g, 0.660 mol) were sequentially added to the solution from Part A. The reaction was stirred at ambient temperature for three days. The organic layer was separated and washed with water (3 x 200 mL), dried over potassium carbonate, and concentrated under reduced pressure to provide 48.4 g of ethyl 4-[(3-aminoquinolin-4-yl)amino]butanoate as an orange oil.

Part C

A solution of ethoxyacetyl chloride (6.61 g, 54.0 mmol) in dichloromethane (10 mL) was added dropwise to a solution of ethyl 4-[(3-aminoquinolin-4-yl)amino]butanoate (11.8 g, 43.2 mmol) in dichloromethane (150 mL). The reaction was stirred for 30 minutes and then concentrated under reduced pressure. Triethylamine (16.7 g, 165 mmol) and ethanol (150 mL) were added, and the resulting solution was heated at reflux for four hours. The solvent was removed under reduced pressure. Dichloromethane (75 mL) was added, and the resulting solution was washed sequentially with water (3 x 75 mL) and saturated aqueous sodium bicarbonate (75 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide 12.5 g of ethyl 4-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butanoate as a dark oil.

Part D

Ethyl 4-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butanoate (6.25 g, 18.3 mmol) and morpholine (16.0 g, 184 mmol) were sealed and heated in a high-pressure vessel at 130 °C overnight. An analysis by TLC indicated the reaction was incomplete. Pyridinium *p*-toluenesulfonate (100 mg) was added, and the reaction was heated for three days at 105 °C and for one day at 125 °C. The solution was allowed to cool and then poured into water (100 mL). The resulting solution was extracted with dichloromethane (3 x 75 mL), and the combined extracts were dried over potassium carbonate, filtered, and concentrated under reduced pressure. The residue was mixed with ethyl acetate (50 mL) and hexane (200 mL) and sonicated. The solvent was decanted away to afford 6.9 g of 2-(ethoxymethyl)-1-(4-morpholin-4-yl-4-oxobutyl)-1*H*-imidazo[4,5-*c*]quinoline as an oil.

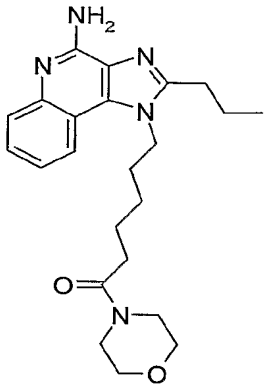
Part E

2-(Ethoxymethyl)-1-(4-morpholin-4-yl-4-oxobutyl)-1*H*-imidazo[4,5-*c*]quinoline (6.9 g, 18 mmol) was treated with mCPBA (7.9 g, 35 mmol), concentrated ammonium hydroxide (50 mL of 29%), and *p*-toluenesulfonyl chloride (6.0 g, 32 mmol) according to a modification of the method described in Part E of Example 3. The mCPBA addition was carried out at 0 °C, and the reaction was carried out in dichloromethane (150 mL). The crude product was triturated with 2:1 ethyl acetate:hexane (15 mL), and the resulting solid was isolated by filtration, washed with 30:70 ethyl acetate:hexane, recrystallized twice from methanol:water, and dried overnight in a vacuum oven at 70 °C to provide 2-(ethoxymethyl)-1-(4-morpholin-4-yl-4-oxobutyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as yellow crystals, mp 201-203 °C.

Anal. Calcd for $C_{21}H_{27}N_5O_3$: C, 63.46; H, 6.85; N, 17.62. Found: C, 63.24; H, 6.84; N, 17.54.

Example 6

1-(6-Morpholin-4-yl-6-oxohexyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

Anhydrous ethanol (400 mL) was cooled to -78 °C, and thionyl chloride (63.34 mL, 868.4 mmol) was added. The reaction was stirred for one hour at -78 °C, and solid 6-aminocaproic acid (100.0 g, 723.7 mmol) was then added. The reaction was allowed to warm to ambient temperature slowly, stirred overnight, and then concentrated under reduced pressure. The residue was recrystallized from ethyl acetate:diethyl ether to provide 137 g of ethyl 6-aminocaproate hydrochloride as a white solid.

Part B

Potassium carbonate (6.62 g, 47.9 mmol) and triethylamine (16.7 mL, 0.120 mol) were sequentially added with stirring to a solution of 4-chloro-3-nitroquinoline (10.0 g, 47.9 mmol) in chloroform (200 mL). After 15 minutes, ethyl 6-aminocaproate hydrochloride (11.23 g, 57.52 mmol) was slowly added, and the reaction was stirred for two hours; washed sequentially with water (200 mL), saturated aqueous sodium bicarbonate, and brine; dried over magnesium sulfate; filtered; concentrated under reduced pressure; and used in Part C without purification.

Part C

The material from Part B was hydrogenated according to the method described in Part C of Example 1 to provide 15.0 g of ethyl 6-[(3-aminoquinolin-4-yl)amino]hexanoate.

Part D

Trimethyl orthobutyrate (15.0 g, 49.8 mmol) and pyridinium *p*-toluenesulfonate (0.20 g, 0.80 mmol) were added to a solution ethyl 6-[(3-aminoquinolin-4-yl)amino]hexanoate (15.0 g, 49.8 mmol) in toluene (400 mL), and the reaction was heated at reflux under a Dean-Stark trap for 4.5 hours while the distillate was periodically removed. The reaction was allowed to cool to ambient temperature, washed sequentially with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide ethyl 6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoate, which was used without purification.

Part E

A solution of sodium hydroxide (4.35 g, 109 mmol) in water (50 mL) was added to a solution of the material from Part D in ethanol (100 mL), and the reaction was stirred at ambient temperature for three hours. Additional sodium hydroxide (2.2 g, 55 mmol) was added, and the reaction was stirred for an additional hour and then concentrated under reduced pressure. The residue was diluted with water (100 mL) and adjusted to pH 5 with the addition of 10% hydrochloric acid. The mixture was extracted three times with chloroform, and the combined extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 12.4 g of 6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoic acid.

Part F

A solution of 6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoic acid (3.0 g, 9.2 mmol) in anhydrous dichloromethane (50 mL) was cooled to 0 °C. Oxalyl chloride (1.44 mL, 16.6 mmol) was added dropwise over a period of 15 minutes. The resulting solution was allowed to warm to ambient temperature and stirred for one hour and then concentrated under reduced pressure. The residue was dissolved in dichloromethane (50 mL), and morpholine (2.41 mL, 27.6 mmol) was added. The reaction was stirred overnight, washed sequentially with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 3.6 g of 1-(6-morpholin-4-yl-6-oxohexyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinoline.

Part G

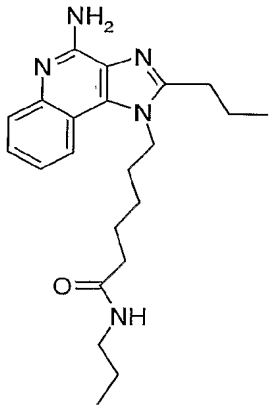
Under a nitrogen atmosphere, a solution of 1-(6-morpholin-4-yl-6-oxohexyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinoline (3.6 g, 9.1 mmol) in chloroform (100 mL) was treated

with mCPBA (6.29 g, 36.5 mmol). The reaction was stirred for two hours, washed sequentially with saturated aqueous sodium bicarbonate (3 x) and brine, dried over magnesium sulfate, and filtered. Concentrated ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (2.60 g, 13.7 mmol) were added sequentially to the filtrate. The reaction was stirred vigorously for two hours, and then the organic layer was separated and washed sequentially with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with 95:5 dichloromethane:methanol) followed by recrystallization from ethyl acetate:hexane to provide 0.84 g of 1-(6-morpholin-4-yl-6-oxohexyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as brown needles, mp 149-151 °C.

Anal. Calcd for $C_{23}H_{31}N_5O_2$: C, 67.46; H, 7.63; N, 17.12. Found: C, 67.28; H, 7.56; N, 16.75.

Example 7

6-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylhexanamide



Part A

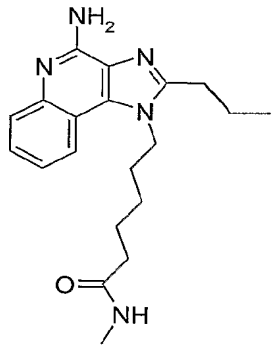
6-(2-Propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoic acid (3.0 g, 9.2 mmol, prepared in Parts A through E of Example 6) was treated with oxalyl chloride (1.45 mL, 16.6 mmol) and *n*-propylamine (2.27 mL, 27.6 mmol) according to the method described in Part F of Example 6 to provide 3.4 g of *N*-propyl-6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanamide. The acid chloride solution was cooled to 0 °C before the addition of *n*-propylamine.

Part B

mCPBA (6.4 g, 37.1 mmol) was added to a solution of the material from Part A in chloroform (75 mL). The reaction was stirred for two hours, washed sequentially with saturated aqueous sodium bicarbonate (2 x) and brine, dried over magnesium sulfate, and filtered. Concentrated ammonium hydroxide (40 mL) was added to the filtrate. The mixture was stirred for ten minutes before the addition of *p*-toluenesulfonyl chloride (2.65 g, 13.9 mmol). The reaction was stirred vigorously for two hours, and then the organic layer was separated and washed sequentially with 10% sodium hydroxide (2 x) and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with dichloromethane:methanol in a gradient from 97:3 to 95:5) followed by recrystallization from methanol:water to provide 0.45 g of 6-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylhexanamide as brown needles, mp 139-141°C.
Anal. Calcd for $C_{22}H_{31}N_5O \cdot 0.44\ H_2O$: C, 67.85; H, 8.25; N, 17.98. Found: C, 67.80; H, 8.22; N, 17.82.

Example 8

6-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methylhexanamide



Part A

A solution of sodium hydrosulfite (73.55 g, 422.4 mmol) and potassium carbonate (65.9 g, 476 mmol) in water (200 mL) was stirred for 15 minutes. A mixture of ethyl 6-(3-nitroquinolin-4-ylamino)hexanoate (40.0 g, 121 mmol, prepared as described in Parts A and B of Example 6), 1,1'-di-*n*-octyl-4,4'-bipyridinium dibromide (0.65 g, 1.2 mmol), dichloromethane (200 mL), and water (40 mL) was added over a period of five minutes, and the reaction was stirred overnight at ambient temperature. Water (100 mL) was

added; the organic layer was separated and washed with water (3 x 150 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide 25.15 g of ethyl 6-[(3-aminoquinolin-4-yl)amino]hexanoate. The product was mixed with material from another run.

Part B

A solution of ethyl 6-[(3-aminoquinolin-4-yl)amino]hexanoate (44.0 g, 146 mmol) in toluene (500 mL) was heated at reflux under a Dean-Stark trap for 1.5 hours and then allowed to cool to ambient temperature. Trimethyl orthobutyrate (29.2 mL, 182.5 mmol) and pyridinium *p*-toluenesulfonate (0.300 g, 1.20 mmol) were sequentially added, and the reaction was heated at reflux for three hours, allowed to cool to ambient temperature, and concentrated under reduced pressure. The residue was dissolved in dichloromethane, and the resulting solution was washed sequentially with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with 97:3 dichloromethane:methanol) to provide 38 g of ethyl 6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoate.

Part C

The method described in Part D of Example 3 was used to treat ethyl 6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoate (5.0 g, 14 mmol) with methylamine (8 mL of a 40% solution). The reaction was complete after being stirred overnight at 70 °C. Following the work-up procedure, 3.42 g of *N*-methyl-6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanamide were obtained.

Part D

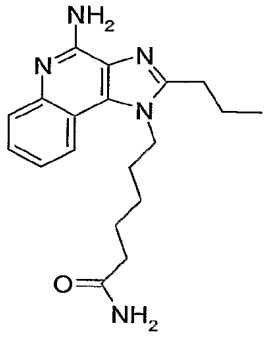
mCPBA (5.0 g, 29.03 mmol) was added to a solution of *N*-methyl-6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanamide (3.42 g, 9.67 mmol) in chloroform (100 mL). The reaction was stirred for two hours at ambient temperature and then washed with 10% aqueous sodium hydroxide. Ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (2.39 g, 12.6 mmol) were sequentially added, and the reaction was stirred vigorously for two hours. The organic layer was separated and washed sequentially with 10% sodium hydroxide, saturated aqueous sodium bicarbonate, and brine; dried over magnesium sulfate; filtered; and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with 95:5

dichloromethane:methanol) followed by recrystallization from methanol:water to provide 1.055 g of 6-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methylhexanamide as beige needles, mp 158-159 °C.

Anal. Calcd for $C_{20}H_{27}N_5O$: C, 67.96; H, 7.70; N, 19.81. Found: C, 67.65; H, 7.45; N, 19.74.

Example 9

6-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanamide



Part A

A solution ethyl 6-[(3-aminoquinolin-4-yl)amino]hexanoate (25.15 g, 83.4 mmol, prepared in Part A of Example 8) in toluene (400 mL) was treated with trimethyl orthobutyrate (15.4 mL, 96.2 mmol) and pyridinium *p*-toluenesulfonate (0.20 g, 0.80 mmol) according to a modification of the method described in Part D of Example 6. The reaction was not complete after five hours and was allowed to cool to ambient temperature overnight. Additional pyridinium *p*-toluenesulfonate (0.20 g, 0.80 mmol) and trimethyl orthobutyrate (2.0 mL, 12 mmol) were added. The reaction was heated at reflux for two hours and then subjected to the work-up procedure to provide 25.0 g of ethyl 6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoate.

Part B

Ammonium acetate (20 g) and ethyl 6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoate (4.11 g, 11.6 mmol) were heated overnight at 140 °C in a sealed vessel. The reaction was allowed to cool to ambient temperature, and saturated aqueous sodium bicarbonate was added. The mixture was extracted with chloroform (3 x), and the extracts were combined and concentrated under reduced pressure. The crude product was purified

by column chromatography on silica gel (eluting with 95:5 dichloromethane:methanol) to provide 1.7 g of 6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanamide.

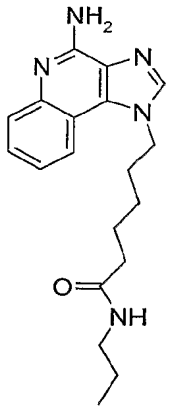
Part C

6-(2-Propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanamide (1.7 g, 5.2 mmol) was treated with mCPBA (3.61 g, 15.7 mmol) followed by ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (1.49 g, 7.84 mmol) according to the method described in Part D of Example 8. The crude product was purified as described in Part D of Example 8 to provide 0.137 g of 6-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanamide as tan needles, mp 210-211°C.

Anal. Calcd for $C_{19}H_{25}N_5O$: C, 67.23; H, 7.42; N, 20.63. Found: C, 66.95; H, 7.76; N, 20.43.

Example 10

6-(4-Amino-1*H*-imidazo[4,5-*c*]quinolin–1-yl)-*N*-propylhexanamide



Part A

Triethyl orthoformate (12.74 mL, 76.64 mmol) and pyridinium *p*-toluenesulfonate (0.200 g) were sequentially added to a solution of ethyl 6-[(3-aminoquinolin-4-yl)amino]hexanoate (16.5 g, 54.7 mmol, prepared as described in Part A of Example 8) in toluene (200 mL), and the reaction was heated at reflux under a Dean-Stark trap for four hours, allowed to cool to ambient temperature, and concentrated under reduced pressure. The residue was dissolved in dichloromethane, and the resulting solution was washed sequentially with saturated aqueous sodium bicarbonate and brine, dried over magnesium

sulfate, filtered, and concentrated under reduced pressure to provide 16.4 g of ethyl 6-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoate.

Part B

A solution of ethyl 6-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoate (7.0 g, 22.5 mmol) and *n*-propylamine (11.1 mL, 135 mmol) in THF (10 mL) was heated at 100 °C for ten days in a sealed high-pressure vessel. Additional *n*-propylamine (20 mL) was added after three days and again after seven days. After ten days, the reaction was concentrated under reduced pressure to provide 7.0 g of 6-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylhexanamide.

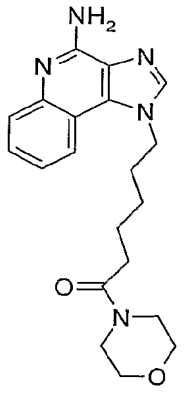
Part C

6-(1*H*-Imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylhexanamide (7.0 g, 26 mmol) was treated with mCPBA (8.68 g, 37.7 mmol) followed by ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (8.01 g, 42.1 mmol) according to the method described in Part D of Example 8. The crude product was triturated with ethyl acetate and recrystallized twice from methanol:water to provide 2.00 g of 6-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylhexanamide as brown needles, mp 128-130 °C.

Anal. Calcd for $C_{19}H_{25}N_5O \cdot 0.20\ H_2O$: C, 66.52; H, 7.46; N, 20.42. Found: C, 66.12; H, 7.38; N, 20.10.

Example 11

1-(6-Morpholin-4-yl-6-oxohexyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

A solution of sodium hydroxide (1.66 g, 41.7 mmol) in water (15 mL) was added to a solution of ethyl 6-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoate (10.0 g, 32.1 mmol, prepared in Part A of Example 10) in ethanol (75 mL), and the reaction was stirred at ambient temperature for two hours and then concentrated under reduced pressure. The residue was diluted with water and adjusted to pH 5 with the addition of 10% hydrochloric acid. The mixture was extracted with dichloromethane, and the combined extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 2.5 g of 6-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoic acid.

Part B

6-(1*H*-Imidazo[4,5-*c*]quinolin-1-yl)hexanoic acid (2.5 g, 8.8 mmol) was treated with oxalyl chloride (1.39 mL, 15.9 mmol) and morpholine (2.31 mL, 26.5 mmol) according to a modification of the method described in Part F of Example 6. The reaction with oxalyl chloride was carried out at ambient temperature, and the reaction with morpholine was complete after one hour. Following the work-up procedure, 3.1 g of 1-(6-morpholin-4-yl-6-oxohexyl)-1*H*-imidazo[4,5-*c*]quinoline were obtained.

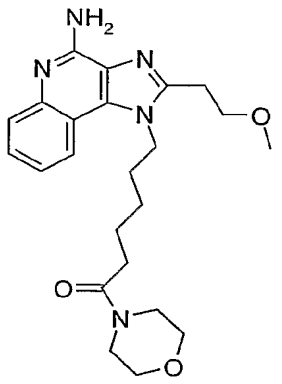
Part C

1-(6-Morpholin-4-yl-6-oxohexyl)-1*H*-imidazo[4,5-*c*]quinoline (3.09 g, 8.79 mmol) was treated with mCPBA (3.54 g, 15.4 mmol) followed by ammonium hydroxide (50 mL) and *p*-toluenesulfonyl chloride (3.26 g, 17.4 mmol) according to the method described in Part D of Example 8. The crude product was purified as described in Part C of Example 10 to provide 0.422 g of 1-(6-morpholin-4-yl-6-oxohexyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as brown needles, mp 166-168 °C.

Anal. Calcd for $C_{20}H_{25}N_5O_2$: C, 65.37; H, 6.86; N, 19.06. Found: C, 65.09; H, 6.75; N, 18.87.

Example 12

2-(2-Methoxyethyl)-1-(6-morpholin-4-yl-6-oxohexyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

Methoxypropionyl chloride (4.85 g, 39.8 mmol) was added dropwise over a period of ten minutes to a solution of ethyl 6-(3-aminoquinolin-4-ylamino)hexanoate (10.0 g, 33.2 mmol, prepared as described in Part A of Example 8) in dichloromethane (200 mL). The reaction was stirred for one hour at ambient temperature and then concentrated under reduced pressure. Triethylamine (18.49 g, 132.7 mmol) and ethanol (200 mL) were added, and the resulting solution was heated at reflux for three hours. The solvent was removed under reduced pressure. Dichloromethane (75 mL) was added, and the resulting solution was washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 12.05 g of ethyl 6-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]hexanoate as a dark oil.

Part B

Ethyl 6-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]hexanoate (12.05 g, 32.61 mmol) was treated with sodium hydroxide (1.70 g, 42.4 mmol) according to a modification of the method described in Part A of Example 11. The reaction was stirred overnight at ambient temperature to provide 8.35 g of 6-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]hexanoic acid after the aqueous work-up procedure.

Part C

6-[2-(2-Methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]hexanoic acid (4.1 g, 12 mmol) was treated with oxalyl chloride (1.89 mL, 21.6 mmol) and morpholine (3.15 mL, 36.0 mmol) according to a modification of the method described in Part F of Example 6. The reaction with oxalyl chloride was carried out at ambient temperature, and the reaction

with morpholine was complete after two hours. Following the work-up procedure, 4.55 g of 2-(2-methoxyethyl)-1-(6-morpholin-4-yl-6-oxohexyl)-1*H*-imidazo[4,5-*c*]quinoline were obtained.

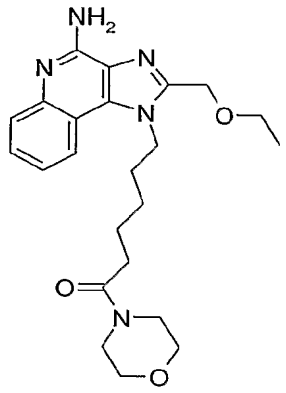
Part D

2-(2-Methoxyethyl)-1-(6-morpholin-4-yl-6-oxohexyl)-1*H*-imidazo[4,5-*c*]quinoline (4.55 g, 11.1 mmol) was treated with mCPBA (4.97 g, 21.6 mmol) followed by ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (3.69 g, 19.4 mmol) according to the method described in Part D of Example 8. The crude product was recrystallized twice from ethyl acetate to provide 1.17 g of 2-(2-methoxyethyl)-1-(6-morpholin-4-yl-6-oxohexyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as brown needles, mp 131-132 °C.

Anal. Calcd for $C_{23}H_{31}N_5O_3 \cdot 0.14\ H_2O$: C, 64.54; H, 7.37; N, 16.36. Found: C, 64.14; H, 7.43; N, 16.40.

Example 13

2-(Ethoxymethyl)-1-(6-morpholin-4-yl-6-oxohexyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

Ethyl 6-(3-nitroquinolin-4-ylamino)hexanoate (27.1 g, 81.8 mmol, prepared as described in Parts A and B of Example 6) was treated with sodium hydrosulfite (49.8 g, 286 mmol), potassium carbonate (44.6 g, 323 mmol), and ethyl viologen dibromide (0.306 g, 0.818 mmol) according to a modification of the method described in Part A of Example 8. After the reaction was stirred overnight, additional sodium hydrosulfite (5.0 g, 29 mmol) was added, and the reaction was stirred for one additional hour. The organic layer

was separated, washed three times with water, and concentrated under reduced pressure to provide 24 g of ethyl 6-(3-aminoquinolin-4-ylamino)hexanoate.

Part B

A solution of ethyl 6-(3-aminoquinolin-4-ylamino)hexanoate (9.25 g, 30.7 mmol) in chloroform (100 mL) was cooled to 0 °C; triethylamine (5.13 mL, 36.8 mmol) was added. Ethoxyacetyl chloride (4.51 g, 36.8 mmol) was then added dropwise over a period of five minutes. The reaction was allowed to warm to ambient temperature, heated at reflux overnight, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with 93:7 dichloromethane:methanol) to provide 7.73 g of ethyl 6-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoate.

Part C

A solution of ethyl 6-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoate (4.0 g, 11 mmol) in morpholine (7 mL) was heated at reflux for three days, allowed to cool to ambient temperature, and concentrated under reduced pressure. The residue was dissolved in dichloromethane; the resulting solution was washed sequentially with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, and concentrated under reduced pressure to provide 4.4 g of 2-(ethoxymethyl)-1-(6-morpholin-4-yl-6-oxohexyl)-1*H*-imidazo[4,5-*c*]quinoline.

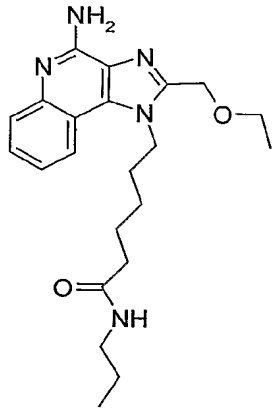
Part D

2-(Ethoxymethyl)-1-(6-morpholin-4-yl-6-oxohexyl)-1*H*-imidazo[4,5-*c*]quinoline (4.4 g, 11 mmol) was treated with mCPBA (5.54 g, 32.1 mmol) followed by ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (2.74 g, 14.4 mmol) according to the method described in Part D of Example 8. The crude product was purified as described in Part D of Example 8 and then dried for two days at 60 °C to provide 1.061 g of 2-(ethoxymethyl)-1-(6-morpholin-4-yl-6-oxohexyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a beige powder, mp 160-162 °C.

Anal. Calcd for $C_{23}H_{31}N_5O_3 \cdot 0.47\ H_2O$: C, 63.65; H, 7.42; N, 16.14. Found: C, 63.64; H, 7.42; N, 16.05.

Example 14

6-[4-Amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-*N*-propylhexanamide



Part A

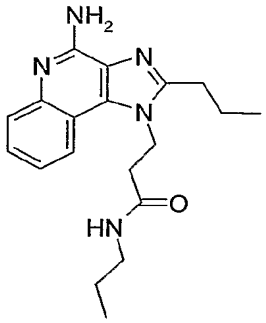
A solution of ethyl 6-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoate (3.73 g, 10.1 mmol, prepared in Parts A and B of Example 13), *n*-propylamine (5 mL), and THF (5 mL) was heated at 80 °C for three days in a high-pressure vessel, allowed to cool to ambient temperature, and concentrated under reduced pressure. The work-up procedure described in Part C of Example 13 was followed to provide 4.1 g of 6-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-*N*-propylhexanamide.

Part B

6-[2-(Ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-*N*-propylhexanamide (4.1 g, 11 mmol) was treated with mCPBA (5.74 g, 33.3 mmol) followed by ammonium hydroxide (50 mL) and *p*-toluenesulfonyl chloride (2.85 g, 14.9 mmol) according to the method described in Part D of Example 8. The crude product was purified by column chromatography on silica gel (eluting with 97:3 dichloromethane:methanol) followed by recrystallization from methanol:water to provide 0.548 g of 6-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-*N*-propylhexanamide as beige needles, mp 161-162 °C. Anal. Calcd for $C_{22}H_{31}N_5O_2$: C, 66.47; H, 7.86; N, 17.62. Found: C, 66.27; H, 7.94; N, 17.38.

Example 15

3-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylpropanamide



Part A

Potassium carbonate (19.87 g, 143.8 mmol) and triethylamine (50.1 mL, 359 mmol) were sequentially added with stirring to a solution of 4-chloro-3-nitroquinoline (30.0 g, 144 mmol) in chloroform (200 mL). After 15 minutes, β-alanine ethyl ester hydrochloride (26.5 g, 173 mmol) was slowly added, and the reaction was stirred overnight at ambient temperature. Water (100 mL) was added, and the mixture was stirred for 15 minutes. The organic layer was separated, washed sequentially with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 27.4 g of ethyl *N*-(3-nitroquinolin-4-yl)-β-alaninate as a yellow solid, which was used without purification.

Part B

Ethyl *N*-(3-nitroquinolin-4-yl)-β-alaninate (28.2 g, 97.5 mmol) was treated with sodium hydrosulfite (50.9 g, 292 mmol), potassium carbonate (53.2 g, 385 mmol), and ethyl viologen dibromide (0.364 g, 0.973 mmol) according to a modification of the method described in Part A of Example 8. After the reaction was stirred overnight, additional sodium hydrosulfite (5.0 g, 29 mmol) was added, and the reaction was stirred for two additional hours. Additional sodium hydrosulfite (2.0 g, 5.3 mmol) was added, and the reaction was stirred for one additional hour. An analysis by TLC indicated the reaction was complete. The organic layer was separated, washed three times with water, and concentrated under reduced pressure to provide 20.7 g of ethyl *N*-(3-aminoquinolin-4-yl)-β-alaninate.

Part C

Ethyl *N*-(3-aminoquinolin-4-yl)-β-alaninate (10.0 g, 38.6 mmol) was treated according to a modification of the method described in Part B of Example 8. After the addition of trimethyl orthobutyrate (7.71 mL, 48.2 mmol) and pyridinium *p*-toluenesulfonate (0.200 g, 0.796 mmol), the reaction was heated at reflux for one hour and subjected to the work-up procedure to provide 12.3 g of ethyl 3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanoate, which was used without purification.

Part D

A solution of ethyl 3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanoate (3.45 g, 11.1 mmol), *n*-propylamine (9.1 mL, 110 mmol), and THF (5 mL) was heated at 80 °C for two days in a high-pressure vessel, allowed to cool to ambient temperature, and concentrated under reduced pressure to provide 3.5 g of 3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylpropanamide.

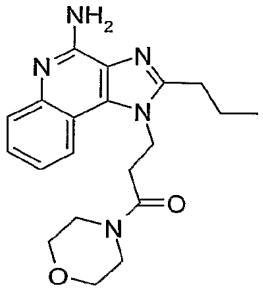
Part E

3-(2-Propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylpropanamide (3.5 g, 11 mmol) was treated with mCPBA (5.85 g, 32.4 mmol) followed by ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (2.76 g, 14.6 mmol) according to a modification of the method described in Part D of Example 8. When the reaction was complete, the organic layer was separated, washed with 10% aqueous sodium bicarbonate, and concentrated under reduced pressure. The crude product was purified as described in Part D of Example 8 to provide 1.026 g of 3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylpropanamide as beige needles, mp 157-158 °C.

Anal. Calcd for $C_{19}H_{25}N_5O \cdot 0.97\ H_2O$: C, 63.94; H, 7.61; N, 19.62. Found: C, 63.95; H, 7.69; N, 19.55.

Example 16

1-(3-Morpholin-4-yl-3-oxopropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

Ethyl *N*-(3-nitroquinolin-4-yl)-β-alaninate (41.6 g, 144 mmol, prepared as described in Part A of Example 15) was treated with sodium hydrosulfite (87.62 g, 503.3 mmol), potassium carbonate (78.5 g, 568 mmol), and ethyl viologen dibromide (0.54 g, 1.4 mmol) according to a modification of the method described in Part A of Example 8. After the reaction was stirred overnight, additional sodium hydrosulfite (5.0 g, 29 mmol) was added, and the reaction was stirred for one additional hour. The organic layer was separated, washed with water (5 x 200 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 33.3 g of ethyl *N*-(3-aminoquinolin-4-yl)-β-alaninate.

Part B

Ethyl *N*-(3-aminoquinolin-4-yl)-β-alaninate (33.3 g, 128 mmol) was treated according to a modification of the method described in Part B of Example 8. After the addition of trimethyl orthobutyrate (25.6 mL, 161 mmol) and pyridinium *p*-toluenesulfonate (0.200 g, 0.796 mmol), the reaction was heated at reflux for two hours and subjected to the work-up procedure to provide 37.1 g of ethyl 3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanoate, which was used without purification.

Part C

A solution of ethyl 3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanoate (4.0 g, 15 mmol) in morpholine (20 mL, 0.2 mol) was heated at reflux for two days, allowed to cool to ambient temperature, and concentrated under reduced pressure to provide 5.2 g of 1-(3-morpholin-4-yl-3-oxopropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinoline.

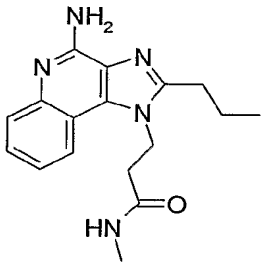
Part D

1-(3-Morpholin-4-yl-3-oxopropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinoline (5.2 g, 15 mmol) was treated with mCPBA (7.64 g, 44.3 mmol) followed by ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (3.79 g, 19.9 mmol) according to the method described in Part D of Example 8. The crude product was purified by column chromatography on silica gel (eluting with 95:5 dichloromethane:methanol) followed by recrystallization from methanol:dichloromethane to provide 0.358 g of 1-(3-morpholin-4-yl-3-oxopropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as yellow needles, mp 172-173 °C.

Anal. Calcd for $C_{20}H_{25}N_5O_2 \cdot 0.2\ CH_3OH \cdot 0.2\ H_2O$: C, 64.27; H, 6.99; N, 18.55. Found: C, 64.20; H, 6.92; N, 18.67.

Example 17

3-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methylpropanamide



Part A

A mixture of ethyl 3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanoate (4.24 g, 16.5 mmol, prepared in Parts A and B of Example 16), THF (15 mL), and methylamine (available as a 40% solution in water, 8 mL) was sealed in a high-pressure vessel, heated at 80 °C overnight, and concentrated under reduced pressure to provide 4.7 g of *N*-methyl-3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanamide.

Part B

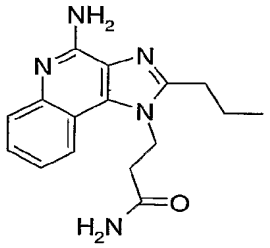
N-Methyl-3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanamide (4.7 g, 13 mmol) was treated with mCPBA (6.58 g, 38.2 mmol) followed by ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (3.27 g, 17.2 mmol) according to the method described in Part D of Example 8. The crude product was purified as described in Part D

of Example 8 to provide 0.674 g of 3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methylpropanamide as a tan powder, mp 177-178 °C.

Anal. Calcd for $C_{17}H_{21}N_5O \cdot 0.22\ H_2O$:C, 64.75; H, 6.85; N, 22.21. Found: C, 65.01; H, 6.97; N, 22.20.

Example 18

3-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanamide hydrochloride



Part A

Ethyl *N*-(3-nitroquinolin-4-yl)-β-alaninate (62.0 g, 214 mmol, prepared as described in Part A of Example 15) was treated with sodium hydrosulfite (130.6 g, 750.1 mmol), potassium carbonate (117 g, 847 mmol), and ethyl viologen dibromide (0.802 g, 2.14 mmol) according to a modification of the method described in Part A of Example 8. After the reaction was stirred overnight, additional water (100 mL), dichloromethane, and sodium hydrosulfite (20.0 g, 115 mmol) were added, and the reaction was stirred for three additional hours. The organic layer was separated; washed with water (6 x), saturated aqueous sodium bicarbonate, and brine; dried over magnesium sulfate; filtered; and concentrated under reduced pressure to provide 40.2 g of ethyl *N*-(3-aminoquinolin-4-yl)-β-alaninate.

Part B

Ethyl *N*-(3-aminoquinolin-4-yl)-β-alaninate (11.0 g, 42.4 mmol) was treated according to a modification of the method described in Part B of Example 8. After the addition of trimethyl orthobutyrate (7.8 mL, 49 mmol) and pyridinium *p*-toluenesulfonate (0.200 g, 0.796 mmol), the reaction was heated at reflux for one hour and subjected to the work-up procedure to provide 10.6 g of ethyl 3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanoate, which was used without purification.

Part C

Ethyl 3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanoate (5.0 g, 16 mmol) was treated with ammonium acetate (25.0 g) according to the method described in Part B of Example 9 to provide 3.9 g of 3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanamide, which was used without purification.

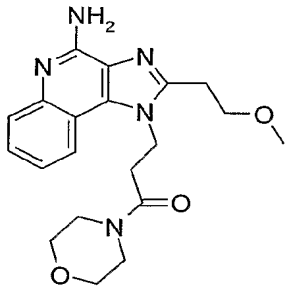
Part D

3-(2-Propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanamide (3.9 g, 14 mmol) was treated with mCPBA (6.19 g, 26.9 mmol) followed by ammonium hydroxide (50 mL) and *p*-toluenesulfonyl chloride (4.6 g, 24 mmol) according to the method described in Part D of Example 8. The crude product was dissolved in methanol, and hydrogen chloride (1.25 mL of a 1 M solution in diethyl ether) was added. The resulting solid was isolated by filtration and dried overnight under high vacuum to provide 0.477 g of 3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanamide hydrochloride as tan needles, mp 242-243 °C.

Anal. Calcd for $C_{16}H_{19}N_5O \cdot 1.0\ HCl \cdot 0.04\ H_2O$: C, 54.82; H, 6.29; N, 19.98. Found: C, 54.81; H, 6.66; N, 19.81.

Example 19

2-(2-Methoxyethyl)-1-(3-morpholin-4-yl-3-oxopropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

The method described in Part A of Example 12 was used to treat ethyl *N*-(3-aminoquinolin-4-yl)-β-alaninate (9.82 g, 37.9 mmol, prepared in Part A of Example 18) with methoxypropionyl chloride (5.54 g, 45.4 mmol). The reaction with triethylamine (21.1 mL, 151 mmol) was heated at reflux for six hours and then subjected to the work-up

procedure to provide 10.3 g of ethyl 3-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propanoate.

Part B

A solution of ethyl 3-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propanoate (4.0 g, 15 mmol), morpholine (13.49 mL, 154.3 mmol), and 2-methyltetrahydrofuran (10 mL) was heated for three days in a high-pressure vessel at 120 °C, allowed to cool to ambient temperature, and concentrated under reduced pressure to provide 5.6 g of 2-(2-methoxyethyl)-1-(3-morpholin-4-yl-3-oxopropyl)-1*H*-imidazo[4,5-*c*]quinoline.

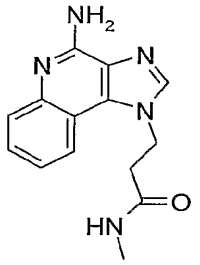
Part C

2-(2-Methoxyethyl)-1-(3-morpholin-4-yl-3-oxopropyl)-1*H*-imidazo[4,5-*c*]quinoline (4.7 g, 13 mmol) was treated with mCPBA (5.73 g, 24.9 mmol) followed by ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (4.23 g, 22.2 mmol) according to the method described in Part D of Example 8. The crude product was recrystallized twice from ethyl acetate to provide 0.233 g of 2-(2-methoxyethyl)-1-(3-morpholin-4-yl-3-oxopropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as beige needles, mp 125-126 °C.

Anal. Calcd for $C_{20}H_{25}N_5O_3 \cdot 0.29\ H_2O$: C, 61.81; H, 6.63; N, 18.02. Found: C, 61.57; H, 6.45; N, 17.76.

Example 20

3-(4-Amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methylpropanamide



Part A

The method described in Part A of Example 10 was used to treat ethyl *N*-(3-aminoquinolin-4-yl)-β-alaninate (10.0 g, 38.6 mmol, prepared in Part A of Example 18) with triethyl orthoformate (8.98 mL, 54.0 mmol). The reaction was complete in three

hours. The reaction mixture was filtered to remove a precipitate and then subjected to the work-up procedure to provide 9.7 g of ethyl 3-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanoate.

Part B

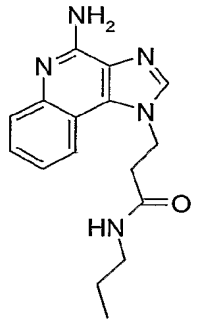
A mixture of ethyl 3-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanoate (4.70 g, 17.5 mmol), THF (5 mL), and methylamine (available as a 40% solution in water, 10 mL) was sealed in a high-pressure vessel, stirred at 100 °C overnight, and concentrated under reduced pressure to provide 4.4 g of 3-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methylpropanamide.

Part C

mCPBA (8.95 g, 38.9 mmol) was added to a solution of 3-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methylpropanamide (4.4 g, 15.6 mmol) in chloroform (100 mL); the reaction was stirred for one hour at ambient temperature. Ammonium hydroxide (40 mL) was added, and the mixture was stirred vigorously for 15 minutes. *p*-Toluenesulfonyl chloride (5.94 g, 31.2 mmol) was added over a period of ten minutes, and the reaction was stirred for two hours. The reaction mixture was filtered to remove a precipitate, and the organic layer was separated and washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was recrystallized from methanol to provide 0.535 g of 3-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methylpropanamide as off-white needles, mp > 260 °C. Anal. Calcd for $C_{14}H_{15}N_5O \cdot 0.13\ H_2O$: C, 61.90; H, 5.66; N, 25.78. Found: C, 61.51; H, 5.39; N, 25.41.

Example 21

3-(4-Amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylpropanamide



Part A

Ethyl 3-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanoate (3.75 g, 13.9 mmol, prepared as described in Part A of Example 20) was treated with *n*-propylamine (11.4 mL, 139 mmol) according to the method described in Part B of Example 20 to provide 3.9 g of 3-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylpropanamide.

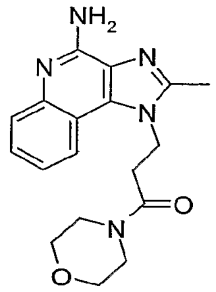
Part B

mCPBA (5.6 g, 24 mmol) was added to a solution of 3-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylpropanamide (3.9 g, 14 mmol) in chloroform (100 mL). The reaction was stirred for two hours and washed with saturated aqueous sodium bicarbonate. Concentrated ammonium hydroxide (40 mL) was added. The mixture was stirred vigorously for five minutes before the addition of *p*-toluenesulfonyl chloride (5.13 g, 26.9 mmol). The reaction was stirred vigorously for two hours, and then the organic layer was separated and washed sequentially with saturated aqueous sodium bicarbonate (2 x) and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was recrystallized three times from ethyl acetate to provide 0.496 g of 3-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylpropanamide as a brown powder, mp 212-214 °C.

Anal. Calcd for $C_{16}H_{19}N_5O \cdot 0.04\ H_2O$: C, 64.47; H, 6.45; N, 23.49. Found: C, 64.09; H, 6.64; N, 23.52.

Example 22

2-Methyl-1-(3-morpholin-4-yl-3-oxopropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

4-Chloro-3-nitroquinoline (76.1 g, 365 mmol) was treated with β-alanine ethyl ester hydrochloride (50.0 g, 326 mmol) in the presence of triethylamine (94.5 mL, 678 mmol) and potassium carbonate (37.45 g, 271.2 mmol) according to a modification of the method described in Part A of Example 15. Before the addition of β-alanine ethyl ester hydrochloride, the reaction was cooled to 0 °C. After this addition, the reaction was stirred for four hours at ambient temperature and subjected to the work-up procedure to provide 105 g of ethyl *N*-(3-nitroquinolin-4-yl)-β-alaninate.

Part B

Ethyl *N*-(3-nitroquinolin-4-yl)-β-alaninate (50.0 g, 173 mmol) was hydrogenated in the presence of 5% platinum on carbon (1.0 g) according to the method described in Part C of Example 1. The reaction was allowed to proceed overnight under hydrogen pressure (40 psi, 2.8 x 10^5 Pa) and then subjected to the work-up procedure to provide 42.3 g of ethyl *N*-(3-aminoquinolin-4-yl)-β-alaninate.

Part C

Ethyl *N*-(3-aminoquinolin-4-yl)-β-alaninate (15.0 g, 57.8 mmol) was treated with trimethyl orthoacetate (10.3 mL, 81.0 mmol) and pyridinium *p*-toluenesulfonate (0.200 g) according to the method described in Part A of Example 10 to provide 14.0 g of ethyl 3-(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanoate as a brown solid.

Part D

A solution of ethyl 3-(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanoate (4.0 g, 15 mmol) and morpholine (10 mL, 100 mmol) was heated for three days in a high-pressure vessel at 100 °C, allowed to cool to ambient temperature, and concentrated under

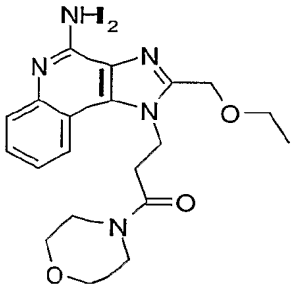
reduced pressure. The residue was dissolved in dichloromethane, and the resulting solution was washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 4.8 g of 2-methyl-1-(3-morpholin-4-yl-3-oxopropyl)-1*H*-imidazo[4,5-*c*]quinoline.

Part E

2-Methyl-1-(3-morpholin-4-yl-3-oxopropyl)-1*H*-imidazo[4,5-*c*]quinoline (4.8 g, 15 mmol) was treated with mCPBA (5.95 g, 25.9 mmol) followed by ammonium hydroxide (50 mL) and *p*-toluenesulfonyl chloride (5.49 g, 28.8 mmol) according to a modification of the method described in Part D of Example 8. The reaction was not washed with 10% aqueous sodium hydroxide prior to the addition of ammonium hydroxide. After the amination reaction was stirred for two hours, water was added. Following the work-up procedure, the chromatographic purification was carried out eluting with 90:10 dichloromethane:methanol. The resulting product was triturated with ethyl acetate and isolated by filtration to provide 2-methyl-1-(3-morpholin-4-yl-3-oxopropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as brown needles, mp 166-169 °C. Anal. Calcd for $C_{18}H_{21}N_5O_2 \cdot 0.50\ H_2O$: C, 62.05; H, 6.36; N, 20.10. Found: C, 61.67; H, 6.63; N, 19.93.

Example 23

2-(Ethoxymethyl)-1-(3-morpholin-4-yl-3-oxopropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

Ethyl *N*-(3-aminoquinolin-4-yl)-β-alaninate (20.0 g, 77.3 mmol, prepared in Parts A and B of Example 22) was treated with ethoxyacetyl chloride (11.29 g, 92.5 mmol) according to a modification the method described in Part A of Example 12. The reaction in dichloromethane (300 mL) was stirred for 1.5 hours, and after the addition of triethylamine (43.08 mL, 309.1 mmol) and ethanol (300 mL), the reaction was heated at

reflux for four hours and then subjected to the work-up procedure to provide 25.0 g of ethyl 3-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanoate.

Part B

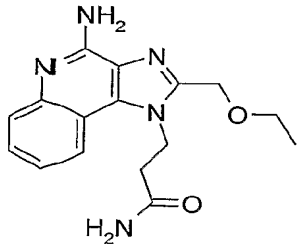
A solution of ethyl 3-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanoate (5.0 g, 15 mmol) and morpholine (10 mL, 100 mmol) was heated overnight in a high-pressure vessel at 90 °C. An analysis by HPLC indicated the reaction was incomplete. The reaction was then heated overnight in a high-pressure vessel at 110 °C, allowed to cool to ambient temperature, and concentrated under reduced pressure to provide 5.1 g of 2-(ethoxymethyl)-1-(3-morpholin-4-yl-3-oxopropyl)-1*H*-imidazo[4,5-*c*]quinoline.

Part C

2-(Ethoxymethyl)-1-(3-morpholin-4-yl-3-oxopropyl)-1*H*-imidazo[4,5-*c*]quinoline (5.1 g, 14 mmol) was treated with mCPBA (5.57 g, 24.2 mmol) followed by ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (5.14 g, 26.9 mmol) according to a modification of the method described in Part D of Example 8. The reaction was not washed with 10% aqueous sodium hydroxide prior to the addition of ammonium hydroxide. The crude product was purified by column chromatography on silica gel (eluting with 90:10 dichloromethane:methanol) and then triturated with ethyl acetate and isolated by filtration to provide 0.843 g of 2-(ethoxymethyl)-1-(3-morpholin-4-yl-3-oxopropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as off-white needles, mp 187-189 °C. Anal. Calcd for $C_{20}H_{25}N_5O_3$: C, 62.65; H, 6.57; N, 18.26. Found: C, 62.28; H, 6.83; N, 18.19.

Example 24

3-[4-Amino-2-(ethoxymethyl)–1*H*-imidazo[4,5-*c*]quinolin-1-yl]propanamide



Part A

Ammonium acetate (7 g) and ethyl 3-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanoate (5.0 g, 15 mmol, prepared in Part A of Example 23) were stirred

overnight at 125 °C in a sealed vessel. The reaction was allowed to cool to ambient temperature, and water (20 mL) was added. A precipitate formed and was isolated by filtration, washed with saturated aqueous sodium bicarbonate, and dried to provide 2.4 g of 3-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propanamide as a tan powder.

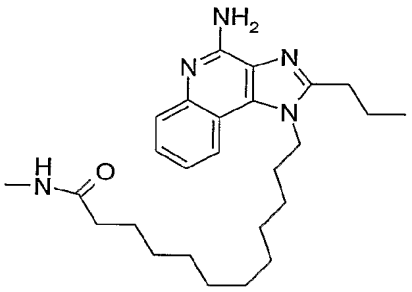
Part B

3-[2-(Ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propanamide (2.4 g, 8.1 mmol) was treated with mCPBA (3.24 g, 14.1 mmol) followed by ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (2.99 g, 15.7 mmol) according to a modification of the method described in Part D of Example 8. The reaction was not washed with 10% aqueous sodium hydroxide prior to the addition of ammonium hydroxide. After the amination reaction was stirred for two hours, 10% aqueous sodium hydroxide (25 mL) and saturated aqueous sodium bicarbonate (25 mL) were sequentially added with stirring. A precipitate formed and was isolated by filtration. The solid was triturated twice with 25% aqueous sodium hydroxide, isolated by filtration, washed with water, and dried in a vacuum oven for three days to provide 0.685 g of 3-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propanamide as tan needles, mp >250 °C.

Anal. Calcd for $C_{16}H_{19}N_5O_2$: C, 61.33; H, 6.11; N, 22.35. Found: C, 61.03; H, 6.11; N, 22.24.

Example 25

12-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methyldodecanamide



Part A

Ethanol (150 mL) was cooled to 0 °C, and thionyl chloride (16.57 mL, 139.3 mmol) was added over a period of ten minutes. The reaction was stirred for ten minutes at 0 °C, and 12-aminododecanoic acid (25.0 g, 116 mol) was then added. The reaction was allowed to warm to ambient temperature, stirred at a slightly elevated temperature for one

hour, and stirred at ambient temperature for two hours. The ethanol was removed under reduced pressure, and the solid residue was recrystallized from ethyl acetate. The crystals were isolated by filtration, washed with diethyl ether, and dried under vacuum to provide 37.4 g of ethyl 12-aminododecanoate hydrochloride as a white solid.

Part B

4-Chloro-3-nitroquinoline (15.52 g, 74.40 mmol) was treated with ethyl 12-aminododecanoate hydrochloride (25.0 g, 89.3 mmol) in the presence of potassium carbonate (10.28 g, 74.38 mmol) and triethylamine (25.9 mL, 186 mmol) according to a modification of the method described in Part A of Example 15. After the reaction was stirred for six hours, an analysis by TLC indicated the presence of starting material, and additional ethyl 12-aminododecanate hydrochloride (1.0 g, 3.6 mmol) was added. The reaction was stirred overnight and subjected to the work-up procedure to provide 31.0 g of ethyl 12-(3-nitroquinolin-4-ylamino)dodecanoate.

Part C

Water (25 mL) and ethyl viologen dibromide (0.279 g, 0.746 mmol) were added to a solution of the material from Part B. Sodium hydrosulfite (45.4 g, 261 mmol) and a solution of potassium carbonate (40.7 g, 295 mmol) in water (200 mL) were added, and the reaction was stirred overnight. An analysis by TLC indicated that the reaction was incomplete. Additional sodium hydrosulfite (5.0 g, 29 mmol) was added, and the reaction was stirred for 0.5 additional hour. The organic layer was separated, washed three times with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide ethyl 12-(3-aminoquinolin-4-ylamino)dodecanoate.

Part D

Ethyl 12-(3-aminoquinolin-4-ylamino)dodecanoate (20.0 g, 51.8 mmol) was treated according to a modification of the method described in Part B of Example 8. Prior to the addition of trimethyl orthobutyrate (9.53 mL, 59.6 mmol) and pyridinium *p*-toluenesulfonate (0.500 g, 1.99 mmol), the reaction was heated at reflux for ten minutes. After the reaction was heated at reflux, it was allowed to cool to ambient temperature, washed sequentially with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, and concentrated under reduced pressure to provide 22.3 g of ethyl 12-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)dodecanoate, which was used without purification.

Part E

A mixture of ethyl 12-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)dodecanoate (4.0 g, 9.1 mmol), THF (5 mL), and methylamine (available as a 40% solution in water, 8 mL) was sealed in a high-pressure vessel and heated at 80 °C overnight. The solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane. The resulting solution was washed sequentially with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 3.8 g of *N*-methyl-12-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)dodecanamide.

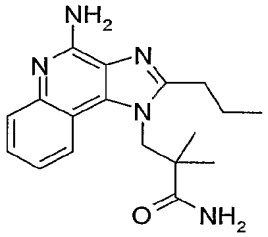
Part F

N-Methyl-12-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)dodecanamide (3.8 g, 9.0 mmol) was treated with mCPBA (4.65 g, 26.9 mmol) followed by ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (2.31 g, 12.1 mmol) according to the method described in Part D of Example 8. The crude product was purified as described in Part D of Example 8 to provide 1.036 g of 12-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methyldodecanamide as a brown crystalline solid, mp 135-137 °C.

Anal. Calcd for $C_{26}H_{39}N_5O$: C, 71.36; H, 8.98; N, 16.0. Found: C, 71. 12; H, 9.18; N, 15.90.

Example 26

3-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanamide



Part A

Concentrated ammonium hydroxide (150 mL of 29%) was cooled to 0 °C in a high-pressure vessel; bromopivalic acid (30.0 g, 359 mmol) was added with stirring over a period of ten minutes. The reaction was stirred for 30 minutes, sealed, heated at 55 °C for three days, and allowed to cool to ambient temperature. The solution was concentrated under reduced pressure, and the residue was dissolved in ethanol (150 mL). The resulting

solution was concentrated under reduced pressure; the residue was dissolved in toluene, which was removed under reduced pressure to provide a white solid.

Part B

The material from Part A was suspended in ethanol (300 mL) and cooled to 0 °C. Thionyl chloride (45.0 mL, 617 mmol) was added dropwise. The reaction was allowed to warm to ambient temperature, stirred overnight, heated at reflux for one hour, and allowed to cool to ambient temperature. The volatiles were removed under reduced pressure, and the residue was mixed with ethyl acetate. The resulting mixture was filtered, and the filtrate was concentrated under reduced pressure to provide ethyl 3-amino-2,2-dimethylpropanoate as a yellow oil, which was used without purification.

Part C

A suspension of 4-chloro-3-nitroquinoline (35.0 g, 168 mmol) and triethylamine (84 mL, 0.60 mol) in dichloromethane (400 mL) was cooled to 0 °C; a solution of ethyl 3-amino-2,2-dimethylpropanoate (40.0 g, 0.220 mol) in dichloromethane (50 mL) was added dropwise. The reaction was stirred at 0 °C for 30 minutes and then at ambient temperature for four hours. The reaction was incomplete as determined by a TLC analysis, and additional ethyl 3-amino-2,2-dimethylpropionate (10.0 g, 55.0 mmol) was added. The reaction was stirred overnight; another analysis by TLC indicated the reaction was incomplete. Additional ethyl 3-amino-2,2-dimethylpropionate (5.0 g, 28 mmol) was added, and the reaction was heated at reflux for three hours. Potassium carbonate (10 g) was added, and the reaction was heated at reflux for two hours and stirred overnight at ambient temperature. Saturated aqueous sodium bicarbonate (50 mL) was added, and the reaction was stirred for three days. The organic layer was separated, washed with water (3 x 100 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide ethyl 2,2-dimethyl-3-[(3-nitroquinolin-4-yl)amino]propanoate as an orange oil, which was mixed with material from another run and used without purification.

Part D

A mixture of ethyl 2,2-dimethyl-3-[(3-nitroquinolin-4-yl)amino]propanoate (59 g), sodium hydrosulfite (109 g, 532 mmol), potassium carbonate (103 g, 744 mmol), and ethyl viologen dibromide (0.50 g, 1.3 mmol), dichloromethane (350 mL), and water (350 mL) was stirred overnight at ambient temperature. The aqueous layer was separated and extracted with dichloromethane (100 mL). The combined organic fractions were washed

with water (4 x 75 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide 46.1 g of ethyl 3-[(3-aminoquinolin-4-yl)amino]-2,2-dimethylpropanoate as a dark oil.

Part E

Ethyl 3-[(3-aminoquinolin-4-yl)amino]-2,2-dimethylpropanoate (8.2 g, 29 mmol) was treated according to a modification of the method described in Part B of Example 8. Prior to the addition of trimethyl orthobutyrate (5.3 g, 36 mmol) and pyridinium *p*-toluenesulfonate (0.10 g, 0.40 mmol), the reaction was heated at reflux for ten minutes. During the work-up procedure, the solution was dried over potassium carbonate. The crude product was purified by column chromatography on silica gel (eluting with 93:7 dichloromethane:methanol containing 3 mL concentrated ammonium hydroxide per liter of eluent) to provide 2.1 g of ethyl 2,2-dimethyl-3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanoate as an orange oil.

Part F

Aqueous sodium hydroxide (1 mL of 50%) was added to a mixture of ethyl 2,2-dimethyl-3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanoate (2.1 g, 6.2 mmol), ethanol (50 mL), and water (5 mL). The reaction was stirred for one hour at ambient temperature and concentrated under reduced pressure. The residue was extracted with dichloromethane (2 x 50 mL); the combined extracts were diluted with dichloromethane (100 mL). The resulting solution was treated with water (10 mL) and adjusted to pH 6 with the addition of concentrated hydrochloric acid (<1 mL). The aqueous layer was separated and extracted with dichloromethane (25 mL). The combined organic fractions were dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide 0.45 g of 2,2-dimethyl-3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionic acid hydrochloride as a yellow oil. The acidic aqueous layer was concentrated under reduced pressure and dried for one hour under vacuum at 55 °C to provide 1.5 g of 2,2-dimethyl-3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanoic acid hydrochloride as a yellow solid.

Part G

A suspension of the oil and the solid from Part F in dichloromethane (100 mL) was cooled to 0 °C, and a solution of oxalyl chloride (1.1 mL, 11 mmol) in dichloromethane (4 mL) was added. After the addition, the reaction was stirred for 30 minutes at ambient temperature and concentrated under reduced pressure. A second treatment with oxalyl

chloride was carried out as described above. The residue was suspended in dichloromethane (75 mL) and cooled to 0 °C. A solution of ammonia (10 mL of 2 M in isopropanol) was then added over a period of two minutes. The reaction was stirred for 30 minutes and then concentrated under reduced pressure. The residue was mixed with dichloromethane (100 mL) and saturated aqueous sodium bicarbonate (25 mL). The aqueous layer was separated and extracted with dichloromethane (50 mL). The combined organic fractions were dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide 1.0 g of 2,2-dimethyl-3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanamide as a yellow solid, which was combined with material from another run.

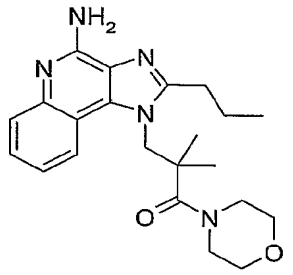
Part H

2,2-Dimethyl-3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanamide was treated with mCPBA (3.24 g, 14.4 mmol) followed by ammonium hydroxide (75 mL)and *p*-toluenesulfonyl chloride (2.5 g, 13 mmol) according to a modification of the method described in Part F of Example 1. The reaction was cooled to 0 °C before the addition of mCPBA. After the addition, the reaction was stirred for 15 minutes at 0 °C and 1.75 hours at ambient temperature. The reaction was not washed prior to the addition of ammonium hydroxide. The amination reaction was stirred for one hour. The crude product was purified by column chromatography on silica gel (eluting with 90:10 dichloromethane:methanol), recrystallized from toluene:methanol, dried overnight in a vacuum oven at 80 °C, recrystallized from acetonitrile:water, and dried overnight in a vacuum oven at 80 °C to provide 0.553 g of 3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanamide as a yellow solid, mp 219-221 °C.

Anal. Calcd for $C_{18}H_{23}N_5O$: C, 66.44; H, 7.12; N, 21.52. Found: C, 66.14; H, 7.04; N, 21.41.

Example 27

1-(2,2-Dimethyl-3-morpholin-4-yl-3-oxopropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

Ethyl 3-[(3-aminoquinolin-4-yl)amino]-2,2-dimethylpropanoate (7.1 g, 25 mmol) was prepared according to the methods described in Parts A through D of Example 26 and treated according to a modification of the method described in Part B of Example 8. Prior to the addition of trimethyl orthobutyrate (4.0 g, 27 mmol) and pyridinium *p*-toluenesulfonate (0.10 g, 0.40 mmol), the reaction was heated at reflux for ten minutes. After the addition, the reaction was heated at reflux for four hours and allowed to stand at ambient temperature overnight. An analysis by TLC indicated the reaction was incomplete, and it was heated at reflux for an additional eight hours and allowed to stand for three days at ambient temperature. Additional pyridinium *p*-toluenesulfonate (0.10 g, 0.40 mmol) was added, and the reaction was heated at reflux for eleven hours and then allowed to cool to ambient temperature. Ethyl acetate (100 mL) was added, and the resulting solution was washed with saturated aqueous sodium bicarbonate (3 x 50 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure to 8 g of ethyl 2,2-dimethyl-3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanoate as a dark oil, which was used without purification.

Part B

A solution of ethyl 2,2-dimethyl-3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanoate (5.1 g, 15 mmol) and morpholine (5 mL, 60 mmol) was heated at reflux overnight. An analysis by LC/MS indicated the reaction was incomplete. The solution was then heated overnight in a high-pressure vessel at 165 °C. Again, an analysis by LC/MS indicated the reaction was incomplete. The volatiles were removed under reduced pressure, and the residue was dissolved in ethanol (30 mL). Aqueous sodium hydroxide

(1.35 mL of 50%, 20.0 mmol) was added, and the reaction was stirred for 1.5 hours. The solution was adjusted to pH 7 with the addition of concentrated hydrochloric acid (~ 1 mL) and then concentrated under reduced pressure. The residue was dissolved in dichloromethane (75 mL); a solution of oxalyl chloride (2.5 mL, 28 mmol) in dichloromethane (5 mL) was added dropwise over a period of two minutes. The reaction was stirred for 30 minutes, and additional oxalyl chloride (0.5 mL, 6 mmol) was added. The reaction was stirred for 30 minutes and diluted with dichloromethane (75 mL). A solution of morpholine (4.0 mL, 41 mmol) in dichloromethane (10 mL) was then added dropwise, and the reaction was stirred for two hours. The reaction was diluted with dichloromethane (45 mL), washed with saturated aqueous sodium bicarbonate (3 x 50 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure. The resulting dark oil was purified by column chromatography on silica gel (eluting with 93:7 dichloromethane:methanol) to provide 5.8 g of 1-(2,2-dimethyl-3-morpholin-4-yl-3-oxopropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinoline as a semi-solid.

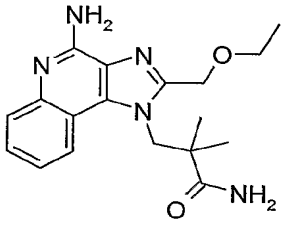
Part C

mCPBA (8.7 g, 39 mmol) was added to a solution of the material from Part B in chloroform (150 mL). The reaction was stirred for 1.75 hours at ambient temperature and then washed with 5% aqueous sodium hydroxide (2 x 50 mL). Ammonium hydroxide (150 mL) and *p*-toluenesulfonyl chloride (4.4 g, 23 mmol) were sequentially added, and the reaction was stirred vigorously for two hours. The aqueous layer was separated and extracted with dichloromethane (50 mL). The combined organic fractions were washed with 5% sodium hydroxide (2 x 50 mL), dried over potassium carbonate, decanted, and concentrated under reduced pressure. The crude product was recrystallized several times from methanol:water to provide 1.84 g of 1-(2,2-dimethyl-3-morpholin-4-yl-3-oxopropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a yellow solid, mp 212-214 °C.

Anal. Calcd for $C_{22}H_{29}N_5O_2 \cdot 0.15\ H_2O$: C, 66.35; H, 7.42; N, 17.59. Found: C, 66.15; H, 7.25; N, 17.82.

Example 28

3-[4-Amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2,2-dimethylpropanamide



Part A

A modification of the method described in Part C of Example 5 was used to treat ethyl 3-[(3-aminoquinolin-4-yl)amino]-2,2-dimethylpropanoate (15.5 g, 60.2 mmol, prepared in Parts A through D of Example 26) with ethoxyacetyl chloride (8.7 g, 71 mmol) followed by triethylamine (24.4 mL, 175 mmol). The reaction with ethoxyacetyl chloride was stirred overnight, and the reaction with triethylamine was heated at reflux in ethanol (125 mL) for four days. Following the work-up procedure, the crude product was purified by column chromatography on silica gel (eluting with dichloromethane:methanol in a gradient from 100:0 to 95:5) to provide 7.9 g of ethyl 3-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2,2-dimethylpropanoate as an oil.

Part B

Aqueous sodium hydroxide (1.5 mL of 50%, 19 mmol) was added to a mixture of ethyl 3-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2,2-dimethylpropanoate (5.0 g, 14 mmol), ethanol (50 mL), and water (5 mL). The reaction was stirred for two hours at ambient temperature; an analysis by TLC indicated that starting material was present. Additional aqueous sodium hydroxide (0.5 mL of 50%) was added, and the reaction was heated at reflux for two hours and concentrated under reduced pressure. Ethanol (100 mL) was added to the residue and then removed under reduced pressure to provide 3-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2,2-dimethylpropanoic acid, which was dried overnight under vacuum.

Part C

A modification of the method described in Part G of Example 26 was used to treat the material from Part B with oxalyl chloride (2 x 2.6 mL, 59.6 mmol) followed by ammonia (5 mL of a 7 M solution in methanol). The reactions were carried out at ambient temperature, and the reaction with ammonia was stirred for two hours. Aqueous sodium

hydroxide (5 mL of 50%) and water (45 mL) were added, and the mixture was stirred. The organic layer was separated, although not completely, and stirred with aqueous sodium hydroxide (10 mL of 25%). The organic fraction was separated and concentrated under reduced pressure to provide 3-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2,2-dimethylpropanamide as a light-brown solid.

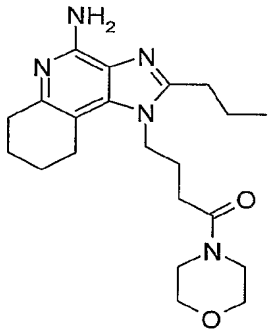
Part D

The material from Part C was treated with mCPBA (5.4 g, 24 mmol) followed by ammonium hydroxide (75 mL)and *p*-toluenesulfonyl chloride (4.1 g, 22 mmol) according to a modification of the method described in Part F of Example 1. The reaction was cooled to 0 °C before the addition of mCPBA. After the addition, the reaction was allowed to warm to ambient temperature and stirred for 2.25 hours. Additional mCPBA (1.5 g, 6.1 mmol) was added, and the reaction was stirred overnight. The reaction was not washed prior to the addition of ammonium hydroxide. The amination reaction was stirred for two hours. The extraction was carried out with dichloromethane (10 x 50 mL). The crude product was purified by column chromatography on silica gel (eluting with dichloromethane:methanol in a gradient from 95:5 to 80:20), recrystallized from ethanol:water, and dried overnight in a vacuum oven at 70 °C to provide 0.417 g of 3-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2,2-dimethylpropanamide as tan crystals, mp 241-243 °C.

Anal. Calcd for $C_{18}H_{23}N_5O_2$: C, 63.32; H, 6.79; N, 20.51. Found: C, 63.21; H, 7.08; N, 20.62.

Example 29

1-(4-Morpholin-4-yl-4-oxobutyl)-2-propyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine

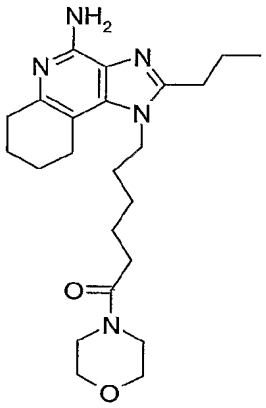


A mixture of 1-(4-morpholin-4-yl-4-oxobutyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (0.62 g, 1.6 mmol, prepared as described in Example 1), platinum (IV) oxide (0.25 g, 1.1 mmol), and trifluoroacetic acid (25 mL) was placed in a Parr vessel and shaken under hydrogen pressure (50 psi, 3.5 x 10^5 Pa) for two hours. An analysis by LC/MS indicated the reaction was incomplete. Additional platinum (IV) oxide (0.5 g) was added, and the reaction was continued overnight. The trifluoroacetic acid was removed under reduced pressure, and the residue was dissolved in methanol (35 mL). Aqueous sodium hydroxide (10 mL of 25%) was added to the solution, and the mixture was stirred for 15 minutes and then diluted with dichloromethane (100 mL). The mixture was filtered through a layer of CELITE filter aid, and the filtrate was concentrated under reduced pressure. The residue was dissolved in dichloromethane, washed with 5% aqueous sodium hydroxide (2 x 25 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure. The resulting solid was recrystallized from water:acetonitrile; the crystals were triturated with 25% aqueous sodium hydroxide for one hour, diluted with water, isolated by filtration, and recrystallized from water:ethanol. The resulting crystals were dried overnight in a vacuum oven at 70 °C to provide 0.5706 g of 1-(4-morpholin-4-yl-4-oxobutyl)-2-propyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine as white crystals, mp 181-183 °C.

Anal. Calcd for $C_{21}H_{31}N_5O_2$: C, 65.43; H, 8.11; N, 18.17. Found: C, 65.36; H, 8.40; N, 18.11.

Example 30

1-(6-Morpholin-4-yl-6-oxohexyl)-2-propyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine



A second batch of 1-(6-morpholin-4-yl-6-oxohexyl)-2-propyl-1*H*–imidazo[4,5-*c*]quinolin-4-amine was prepared according to the methods described in Example 6 with the following modifications. In Part C, a solution of ethyl 6-(3-nitroquinolin-4-ylamino)hexanoate (122.94 g, 371.6 mmol) in dichloromethane (800 mL) was added to a solution of sodium hydrosulfite (226.44 g, 1.30 mol), potassium carbonate (202.86 g, 1.47 mol), and ethyl viologen diiodide (1.737 g, 3.71 mmol) in water (800 mL), and the reaction was stirred overnight at ambient temperature. The organic layer was separated, washed with water (4 x), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 106.7 g of ethyl 6-(3-aminoquinolin-4-ylamino)hexanoate. The crude product from Part G was recrystallized from methanol, triturated with hot ethyl acetate twice, triturated with hexanes, and isolated by filtration to provide 20.9 g of 1-(6-morpholin-4-yl-6-oxohexyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a light tan powder, mp 156-158 °C.

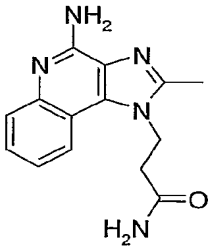
A mixture of 1-(6-morpholin-4-yl-6-oxohexyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (2.0 g, 4.9 mmol), platinum (IV) oxide (1.5 g, 6.6 mmol), and trifluoroacetic acid (50 mL) was placed in a Parr vessel and shaken under hydrogen pressure (50 psi, 3.5×10^5 Pa) for 24 hours. The trifluoroacetic acid was removed under reduced pressure, and the residue was sonicated with 10% aqueous sodium hydroxide. The resulting solid was mixed with material from another run and recrystallized from water. The crystals were isolated by filtration and dried overnight at 80 °C to provide

0.978 g of 1-(6-morpholin-4-yl-6-oxohexyl)-2-propyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white crystaline powder, mp 162-163 °C.

Anal. Calcd for $C_{23}H_{35}N_5O_2$: C, 66.80; H, 8.53; N, 16.93. Found: C, 66.54; H, 8.85; N, 16.87.

Example 31

3-(4-Amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanamide



Part A

Ammonium acetate (4.0 g) and ethyl 3-(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanoate (4.5 g, 17 mmol, prepared as described in Parts A through C of Example 22) were heated for three days at 130 °C in a sealed vessel. The reaction was allowed to cool to ambient temperature, and water was added. The mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluting with dichloromethane:methanol in a gradient from 90:10 to 85:15) to provide 2.20 g of 3-(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanamide as a tan solid.

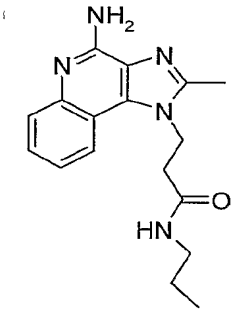
Part B

mCPBA (3.48 g, 15.1 mmol) was added to a solution of 3-(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanamide (2.20 g, 8.65 mmol) in chloroform (100 mL). The reaction was stirred for two hours at ambient temperature and cooled to 0 °C. Ammonium hydroxide (40 mL) was added followed by *p*-toluenesulfonyl chloride (3.21 g, 16.9 mmol), which was added over a period of five minutes. The reaction was stirred for two hours at ambient temperature and then concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with dichloromethane:methanol in a gradient from 90:10 to 80:20). The resulting solid was triturated with 10% aqueous sodium hydroxide, isolated by filtration, washed with water, and dried overnight in a vacuum oven at 60 °C to provide 0.145 g of 3-(4-amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanamide as a off-white powder, mp 237-239 °C.

Anal. Calcd for $C_{14}H_{15}N_5O$: C, 57.78; H, 6.03; N, 24.06. Found: C, 57.38; H, 5.82; N, 24.29.

Example 32

3-(4-Amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylpropanamide



Part A

Ethyl *N*-(3-nitroquinolin-4-yl)-β-alaninate (62.0 g, 214 mmol, prepared as described in Part A of Example 22) was treated with sodium hydrosulfite (130.59 g, 750.04 mmol), potassium carbonate (117 g, 847 mmol), and ethyl viologen dibromide (0.802 g, 2.14 mmol) according to a modification of the method described in Part A of Example 8. After the reaction was stirred overnight, additional water (100 mL), dichloromethane (100 mL) and sodium hydrosulfite (20.0 g, 11.5 mmol) were added, and the reaction was stirred for three additional hours. The organic layer was separated; washed sequentially with water, saturated aqueous sodium bicarbonate, and brine; dried over magnesium sulfate; filtered; and concentrated under reduced pressure to provide 40.2 g of ethyl *N*-(3-aminoquinolin-4-yl)-β-alaninate.

Part B

Ethyl *N*-(3-aminoquinolin-4-yl)-β-alaninate (9.0 g, 35 mmol) was treated with triethyl orthoacetate (8.91 mL, 48.6 mmol) and pyridinium *p*-toluenesulfonate (0.200 g) according to the method described in Part A of Example 10 to provide 6.10 g of ethyl 3-(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanoate. The reaction was complete in two hours, and a precipitate was removed by filtration from the organic layer during the work-up procedure.

Part C

Propylamine (20 mL) and ethyl 3-(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanoate (5.77 g, 20.4 mmol) were heated overnight at 100 °C in a sealed vessel. The reaction was allowed to cool to ambient temperature and concentrated under reduced pressure to provide 6.0 g of 3-(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylpropanamide.

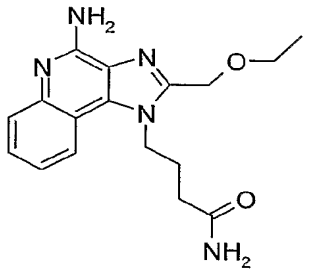
Part D

3-(2-Methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylpropanamide (6.0 g, 20.2 mmol) was treated with mCPBA (8.15 g, 35.4 mmol) followed by ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (7.52 g, 39.5 mmol) according to a modification of the method described in Part D of Example 8. The reaction was not washed with 10% aqueous sodium hydroxide prior to the addition of ammonium hydroxide. The crude product was twice triturated with ethyl acetate and isolated by filtration. The solid was then purified by column chromatography on silica gel (eluting with 90:10 dichloromethane:methanol). The product was then triturated sequentially with 10% aqueous sodium hydroxide and acetone (2 x). The solid was then purified again by column chromatography on silica gel (eluting with dichloromethane:methanol in a gradient from 95:5 to 90:10). The resulting solid was triturated with 10% aqueous sodium hydroxide, isolated by filtration, washed with water, and dried overnight to provide 0.477 g of 3-(4-amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylpropanamide as an off-white powder, mp 188-189 °C.

Anal. Calcd for $C_{17}H_{21}N_5O$: C, 65.57; H, 6.80; N, 22.49. Found: C, 65.24; H, 6.67; N, 22.44.

Example 33

4-[4-Amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butanamide



Part A

Ethyl 4-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butanoate (15.9 g, 46.6 mmol, prepared as described in Parts A through C of Example 5) and ammonium acetate (35.0 g, 455 mmol) were sealed and heated in a high-pressure vessel at 130 °C for two days. An analysis by LC/MS indicated the presence of starting material, and additional ammonium acetate (15 g, 190 mmol) was added. The reaction was heated to 130 °C for several hours, allowed to cool to ambient temperature, stirred for three days, and poured into water (200 mL). Solid sodium bicarbonate was added until the solution was basic. The solution was extracted with dichloromethane (3 x 100 mL, 5 x 75 mL, and then in a continuous extractor for about 20 hours). The extracts were dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide 10.3 g of 4-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butanamide as a light yellow solid.

Part B

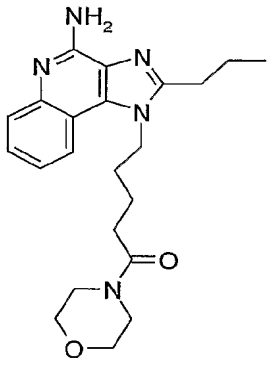
4-[2-(Ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butanamide (4.3 g, 14 mmol) was treated with mCPBA (6.1 g, 27 mmol), concentrated ammonium hydroxide (50 mL of 29%), and *p*-toluenesulfonyl chloride (4.6 g, 24 mmol) according to a modification of the method described in Part E of Example 3. The mCPBA addition was carried out at 0 °C, and the reaction was carried out in dichloromethane (150 mL). At the end of the reaction the layers were separated, and saturated aqueous sodium bicarbonate (100 mL) and 5% aqueous sodium hydroxide (10 mL) were added to the organic layer. The aqueous layer was extracted with dichloromethane (1.3 L), and the combined extracts were dried over potassium carbonate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with 90:10 dichloromethane:methanol containing 4 mL/L of ammonium hydroxide) followed by

recrystallization five times from ethanol containing a small amount of water. The resulting solid was recrystallized from water:acetonitrile (5:1), dried overnight in a vacuum oven at 70 °C, triturated with 25% aqueous ammonium hydroxide, diluted with water, isolated by filtration, recrystallized from ethanol:water, and dried overnight in a vacuum oven at 70 °C to provide 0.4704 g of 4-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butanamide as tan crystals, mp 233-235 °C.

Anal. Calcd for $C_{17}H_{21}N_5O_2 \cdot 0.07\ H_2O$: C, 62.12; H, 6.48; N, 21.31. Found: C, 61.77; H, 6.83; N, 21.22.

Example 34

1-(5-Morpholin-4-yl-5-oxopentyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

Potassium carbonate (66.23 g, 479.3 mmol), triethylamine (167 mL, 1.20 mol), and ethyl 5-aminovalerate hydrochloride (104.4 g, 575.2 mmol) were added to a solution of 4-chloro-3-nitroquinoline (100.0 g, 479.3 mmol) in chloroform (1000 mL) according to the method described in Part B of Example 6. The reaction was run for four hours and provided 151 g of ethyl 5-(3-nitroquinolin-4-ylamino)pentanoate.

Part B

A solution of ethyl 5-(3-nitroquinolin-4-ylamino)pentanoate (151 g, 476 mmol) in dichloromethane (1 L) was added to a solution of sodium hydrosulfite (248.5 g, 1.427 mol), potassium carbonate (259.3 g, 1.876 mol), and ethyl viologen dibromide (1.78 g, 4.75 mmol) in water (1 L), and the reaction was stirred overnight at ambient temperature. An analysis by TLC indicated the presence of starting material; additional sodium hydrosulfite (5.0 g, 29 mmol) was added to the reaction, which was stirred for one

additional hour. The organic layer was separated, washed with water (3 x), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 131.51 g of ethyl 5-(3-aminoquinolin-4-ylamino)pentanoate.

Part C

The method described in Part A of Example 10 was used to treat ethyl 5-(3-aminoquinolin-4-ylamino)pentanoate (26.3 g, 91.5 mmol) with trimethyl orthobutyrate (18.3 mL, 114 mmol) and pyridinium *p*-toluenesulfonate (0.5 g). The reaction was complete in three hours to provide 28 g of ethyl 5-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanoate as a brown oil.

Part D

A solution of sodium hydroxide (2.23 g, 55.9 mmol) in water (100 mL) was added to a solution of ethyl 5-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanoate (14.6 g, 43.0 mmol) in ethanol (100 mL), and the reaction was stirred at ambient temperature overnight, concentrated to remove ethanol, and washed with dichloromethane. The resulting solution was adjusted to pH 5 with the addition of 10% hydrochloric acid. The mixture was extracted twice with chloroform, and the combined extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 11.5 g of 5-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanoic acid.

Part E

A modification of the method described in Part F of Example 6 was used to treat 5-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanoic acid (5.14 g, 16.5 mmol) with oxalyl chloride (2.59 mL, 29.7 mmol) and morpholine (4.33 mL, 49.5 mmol). The oxalyl chloride addition was carried out at ambient temperature, and the reaction with morpholine was complete in three hours. Following the work-up procedure, 6.2 g of 1-(5-morpholin-4-yl-5-oxopentyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinoline were obtained.

Part F

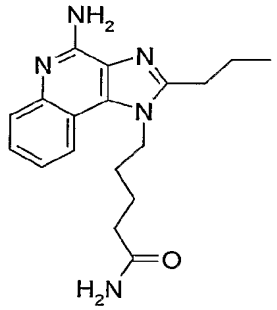
mCPBA (6.56 g, 28.5 mmol) was added to a solution of 1-(5-morpholin-4-yl-5-oxopentyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinoline (6.2 g, 16 mmol) in chloroform (100 mL); the reaction was stirred for three hours at ambient temperature. Ammonium hydroxide (50 mL) was added. *p*-Toluenesulfonyl chloride (6.056 g, 31.76 mmol) was added over a period of five minutes, and the reaction was stirred for one hour. The work-up procedure and chromatographic purification was carried out as described in Part D of

Example 8. The resulting oil was triturated with acetone, isolated by filtration, and dried to provide 1-(5-morpholin-4-yl-5-oxopentyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a tan powder, mp 178-179 °C.

Anal. Calcd for $C_{22}H_{29}N_5O_2$: C, 66.81; H, 7.391; N, 17.71. Found: C, 66.50; H, 7.38; N, 17.41.

Example 35

5-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanamide



Part A

Ethyl 5-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanoate (5.4 g, 15.9 mmol), prepared as described in Parts A through C of Example 34) and ammonium acetate (11.0 g, 143 mmol) were sealed in a high-pressure vessel and heated for two days at 130 °C and then allowed to cool to ambient temperature. Ammonium hydroxide was added to adjust the mixture to a neutral pH. The mixture was then extracted with dichloromethane, and the combined extracts were washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 2.8 g of 5-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanamide, which was combined with material from another run.

Part B

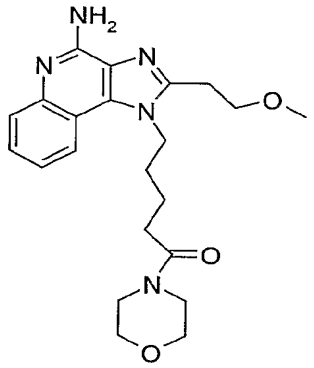
5-(2-Propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanamide (4.4 g, 14 mmol) was treated with mCPBA (4.28 g, 24.8 mmol), ammonium hydroxide (40 mL), and *p*-toluenesulfonyl chloride (5.24 g, 27.4 mmol) according to a modification of the method described in Part F of Example 34. At the completion of the amination reaction, a precipitate was present and was isolated by filtration. The precipitate was triturated and sonicated with acetone, isolated by filtration, and dried in a vacuum oven at 80 °C to

provide 1.28 g of 5-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanamide as a tan powder, mp 202-203 °C.

Anal. Calcd for $C_{18}H_{23}N_5O \cdot 0.09\ H_2O$: C, 66.09; H, 7.15; N, 21.41. Found: C, 65.69; H, 7.46; N, 21.22.

Example 36

2-(2-Methoxyethyl)-1-(5-morpholin-4-yl-5-oxopentyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

Ethyl 5-(3-aminoquinolin-4-ylamino)pentanoate (23.0 g, 88.6 mmol, prepared in Parts A and B of Example 34) was treated according to the method described in Part A of Example 12. The addition of methoxypropionyl chloride (12.97 g, 106.3 mmol) was carried out at 0 °C, and the reaction was stirred at ambient temperature for two hours. The reaction with triethylamine (49.4 g, 354 mmol) was heated at reflux for four hours. After the work-up procedure, 28.6 g of ethyl 5-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]pentanoate were obtained as a brown oil.

Part B

Ethyl 5-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]pentanoate (15.1 g, 42.4 mmol) was treated with sodium hydroxide (2.20 g, 55.2 mmol) according to the method described in Part A of Example 11. The reaction was stirred overnight at ambient temperature to provide 10.2 g of 5-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]pentanoic acid after the aqueous work-up procedure.

Part C

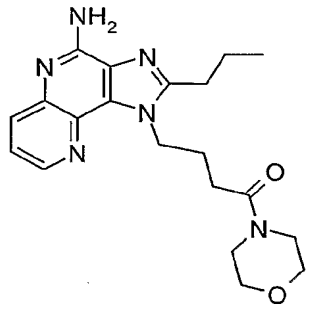
5-[2-(2-Methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]pentanoic acid (5.5 g, 17 mmol) was treated according to a modification of the method described in Part F of Example 6. The reaction with oxalyl chloride (2.63 mL, 30.2 mmol) was carried out at ambient temperature and was complete in 30 minutes. The reaction with morpholine (4.40 mL, 50.4 mmol) was complete after 30 minutes. Following the work-up procedure, 6.5 g of 2-(2-methoxyethyl)-1-(5-morpholin-4-yl-5-oxopentyl)-1*H*-imidazo[4,5-*c*]quinoline were obtained.

Part D

mCPBA (6.60 g, 28.7 mmol) was added to a solution of 2-(2-methoxyethyl)—1-(5-morpholin-4-yl-5-oxopentyl)-1*H*-imidazo[4,5-*c*]quinoline (6.5 g, 17 mmol) in chloroform (100 mL); the reaction was stirred for two hours at ambient temperature. The reaction was cooled to 0 °C, and ammonium hydroxide (50 mL) was added. A solution of benzenesulfonyl chloride (4.11 mL, 33.0 mmol) in chloroform (20 mL) was added over a period of 20 minutes, and the reaction was allowed to warm to ambient temperature and stirred for two hours. The work-up procedure and chromatographic purification was carried out as described in Part D of Example 8. The resulting product was triturated with 10% aqueous sodium hydroxide, isolated by filtration, washed with water, and dried overnight in a vacuum oven to provide 2-(2-methoxyethyl)-1-(5-morpholin-4-yl-5-oxopentyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as an off-white powder, mp 128-129 °C. Anal. Calcd for $C_{22}H_{29}N_5O_3 \cdot 0.17\ H_2O$: C, 63.74; H, 7.13; N, 16.89. Found: C, 63.33; H, 7.34; N, 16.73.

Example 37

1-(4-Morpholin-4-yl-4-oxobutyl)-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine



Part A

A suspension of 4-chloro-3-nitro[1,5]naphthyridine (10.0 g, 47.7 mmol) and ethyl 4-aminobutyrate hydrochloride (9.6 g, 57 mmol) in dichloromethane (200 mL) was cooled to 5 °C. Triethylamine (16.6 mL, 119 mmol) was added, and the reaction was allowed to warm to ambient temperature and stirred for two hours. The mixture was diluted with dichloromethane (200 mL) and washed with saturated aqueous sodium bicarbonate (2 x 150 mL). The combined aqueous fractions were extracted with dichloromethane (100 mL), and the combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 14.5 g of ethyl 4-(3-nitro[1,5]naphthyridin-4-ylamino)butanoate as a yellow solid.

Part B

A mixture of ethyl 4-(3-nitro[1,5]naphthyridin-4-ylamino)butanoate (5.0 g, 16 mmol), 5% platinum on carbon (0.50 g), and ethyl acetate (80 mL) was added to a Parr vessel, and the reaction was placed under hydrogen pressure (30 psi, 2.1 x 10^5 Pa) for 2.5 hours. The reaction mixture was filtered through a layer of CELITE filter agent, and the filter cake was washed with ethyl acetate (50 mL). The filtrate was concentrated under reduced pressure to provide ethyl 4-(3-amino[1,5]naphthyridin-4-ylamino)butanoate as a yellow oil.

Part C

A solution of ethyl 4-(3-amino[1,5]naphthyridin-4-ylamino)butanoate (2.0 g, 7.3 mmol) in dichloromethane (35 mL) was cooled to 0 °C. Butyryl chloride (0.68 mL, 8.0 mmol) was added dropwise over a period of ten minutes, and the reaction was allowed to warm to ambient temperature, stirred for 90 minutes, and concentrated under reduced

pressure. Triethylamine (3.0 mL, 22 mmol) and ethanol (35 mL) were added, and the resulting solution was heated at reflux for two days. Pyridine hydrochloride (0.1 equivalents) was added, and the reaction was heated at reflux overnight. The solvent was removed under reduced pressure, and the residue was partitioned between dichloromethane (70 mL) and saturated aqueous sodium bicarbonate (50 mL). The aqueous layer was separated and extracted with dichloromethane (2 x 25 mL), and the combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 2.43 g of ethyl 4-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]butanoate as a brown oil.

Part D

Aqueous sodium hydroxide (2.4 mL of 6 M) was added to a solution of ethyl 4-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]butanoate (2.37 g, 7.26 mmol) in ethanol (25 mL); the reaction was stirred at ambient temperature for two hours and concentrated under reduced pressure. The residue was dissolved in water (15 mL) and adjusted to pH 4 with the addition of 2 M hydrochloric acid. A precipitate formed, was isolated by filtration, and was mixed with toluene, which was removed under reduced pressure to provide 1.78 g of 4-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]butanoic acid as a tan powder.

Part E

4-(2-Propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]butanoic acid (prepared in a separate run, 5.34 mmol) was treated according to a modification of Part F of Example 6. One drop of *N,N*-dimethylformamide (DMF) was added to the reaction mixture. The addition of oxalyl chloride (1.4 mL, 16 mmol) was carried out at ambient temperature, and the reaction was stirred for two hours. Additional oxalyl chloride (0.5 mL) was added, and the reaction was stirred for an additional hour. The reaction with morpholine (1.17 mL, 13.3 mmol) was stirred for one hour. Following the work-up procedure 1.80 g of 1-(4-morpholin-4-yl-4-oxobutyl)-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridine were obtained as a yellow solid.

Part F

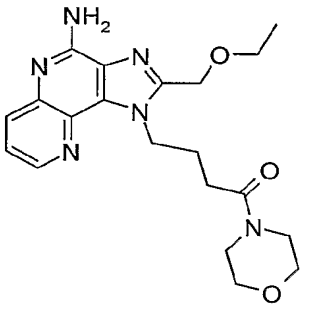
mCPBA (1.18 g, 6.86 mmol) was added to a solution of 1-(4-morpholin-4-yl-4-oxobutyl)-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridine (1.80 g, 4.90 mmol) in chloroform (25 mL); the reaction was stirred for two hours at ambient temperature.

Ammonium hydroxide (10 mL) was added followed by *p*-toluenesulfonyl chloride (1.03 g, 5.39 mmol). The reaction was stirred for one hour and partitioned between saturated aqueous sodium bicarbonate (75 mL) and dichloromethane (70 mL). The aqueous layer was extracted with dichloromethane (2 x 25 mL), and the combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting brown solid was triturated twice with acetonitrile and then purified by column chromatography using a HORIZON HPFC system (an automated, modular high-performance flash purification product available from Biotage, Inc.; Charlottesville, Virginia, USA) using a FLASH 40+M cartridge (also available from Biotage, Inc.). The polar component of the eluent was chloroform:methanol:ammonium hydroxide 80:18:2 (CMA). The purification was carried out eluting with chloroform:CMA in a gradient from 100:0 to 75:25. The resulting solid was dried under high vacuum at 80 °C to provide 0.583 g of 1-(4-morpholin-4-yl-4-oxobutyl)-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine as an off-white powder, mp 196-197 °C.

Anal. Calcd for $C_{20}H_{26}N_6O_2$: C, 62.81; H, 6.85; N, 21.97. Found: C, 62.60; H, 7.06; N, 22.00.

Example 38

2-(Ethoxymethyl)-1-(4-morpholin-4-yl-4-oxobutyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine



Part A

Ethyl 4-(3-amino[1,5]naphthyridin-4-ylamino)butanoate (2.5 g, 9.1 mmol, prepared in Parts A and B of Example 37) was treated with ethoxyacetyl chloride (1.02 mL, 10.0 mmol) and cyclized according to a modification of the method described in Part C of Example 37. The reaction with triethylamine (3.8 mL, 27 mmol) was heated at reflux

overnight and was complete. Following the work-up procedure, 3.11 g of ethyl 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]butanoate were obtained as a brown oil.

Part B

The methods of Parts D and E of Example 37 were used to treat ethyl 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]butanoate (1.0 g, 2.9 mmol) with aqueous sodium hydroxide (2.9 mL of 2 M), oxalyl chloride (0.42 mL, 4.8 mmol), and morpholine (0.35 mL, 4.0 mmol). The reaction with oxalyl chloride was complete within two hours, and no additional reagent was added. Following the work-up procedure 0.64 g of 2-(ethoxymethyl)-1-(4-morpholin-4-yl-4-oxobutyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine was obtained as a yellow solid, which was combined with material from another run.

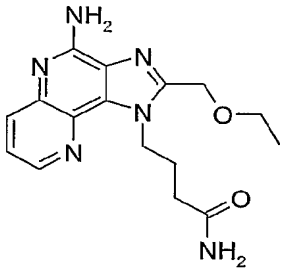
Part C

The method described in Part F of Example 37 was used to treat 2-(ethoxymethyl)-1-(4-morpholin-4-yl-4-oxobutyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine (1.42 g, 3.70 mmol) with mCPBA (0.958 g, 5.55 mmol), ammonium hydroxide (4 mL), and *p*-toluenesulfonyl chloride (0.776 g, 4.07 mmol). Following the chromatographic purification, the resulting solid was dried for 48 hours under high vacuum at 120 °C to provide 0.614 g of 2-(ethoxymethyl)-1-(4-morpholin-4-yl-4-oxobutyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine as a tan powder, mp 156-157 °C.

Anal. Calcd for $C_{20}H_{26}N_6O_3 \cdot 0.3H_2O$: C, 59.48; H, 6.64; N, 20.81. Found: C, 59.55; H, 6.63; N, 20.70.

Example 39

4-[4-Amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]butanamide



Part A

A solution of ammonia in dioxane (33 mL of 0.5 M) was added to a solution of 4-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]butanoyl chloride (4.64 mmol, prepared as described in Parts A and B of Example 38) in dichloromethane (20 mL), and the reaction was stirred overnight at ambient temperature. An analysis by HPLC indicated the reaction was incomplete; ammonia gas was bubbled through the solution for 10 minutes. The reaction was then stirred for one hour and concentrated under reduced pressure. The residue was triturated with water and isolated by filtration to provide 1.02 g of 4-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]butanamide. The filtrate was extracted with dichloromethane (3 x 20 mL), and the combined extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide an additional 0.39 g of product. The combined solids were mixed with material from another run.

Part B

mCPBA (1.80 g, 7.28 mmol) was added to a solution of 4-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]butanamide (1.63 g, 5.20 mmol) in chloroform (50 mL); the reaction was stirred for three hours at ambient temperature. An analysis by LC/MS indicated the reaction was incomplete; therefore, additional mCPBA (1.2 equivalents) was added. The reaction was stirred for two hours and then diluted with saturated aqueous sodium bicarbonate (75 mL) and chloroform (75 mL). The aqueous layer was extracted with dichloromethane (2 x 30 mL) and chloroform (12 x 20 mL), and the combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 2.34 g of 4-[2-(ethoxymethyl)-5-oxido-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]butanamide as an orange solid.

Part C

A solution of the material from Part B in methanol (25 mL) was cooled to 0 °C; ammonium hydroxide (1.8 mL, 26 mmol) was added. Benzenesulfonyl chloride (1.3 mL, 10.4 mmol) was added dropwise, and the reaction was stirred for one hour at 0 °C and concentrated under reduced pressure. The residue was triturated with methanol, isolated by filtration, and dissolved in aqueous sodium hydroxide (20 mL of 2 M). The solution was sonicated to form a precipitate, which was isolated by filtration, washed with cold water, and dried overnight in a vacuum oven at 80 °C to provide 0.432 g of 4-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]butanamide as a pale yellow powder, mp 231-232 °C.

Anal. Calcd for $C_{16}H_{20}N_6O_2 \cdot 0.3H_2O$: C, 57.58; H, 6.22; N, 25.18. Found: C, 57.76; H, 6.39; N, 25.12.

Examples 40-45

Part A

Under a nitrogen atmosphere, triethylamine (47 mL, 340 mmol) was added to a solution of 2,4-dichloro-5,6-dimethyl-3-nitropyridine (30.0 g, 136 mmol) and ethyl 4-aminobutyrate hydrochloride (32 g, 190 mmol) in DMF (500 mL), and the reaction was stirred overnight. The solvent was removed under reduced pressure, and the residue was partitioned between chloroform (500 mL), water (25 mL), and brine (25 mL). The organic layer was separated and washed with water:brine (1:1, 3 x 50 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting orange solid was recrystallized from ethyl acetate:hexanes and dried under high vacuum to provide 21.5 g of ethyl 4-[(2-chloro-5,6-dimethyl-3-nitropyridin-4-yl)amino]butanoate.

Part B

Under a nitrogen atmosphere, a mixture of ethyl 4-[(2-chloro-5,6-dimethyl-3-nitropyridin-4-yl)amino]butanoate (21.5 g, 68 mmol), sodium azide (8.90 g, 136 mmol), cerium(III) chloride heptahydrate (12.7 g, 34 mmol), and 9:1 acetonitrile:water (250 mL) was heated overnight at reflux. The hot reaction mixture was filtered, and the filter cake was washed with acetonitrile. The filtrate was concentrated under reduced pressure, and the residue was triturated with ethyl acetate:hexanes and isolated by filtration to provide 21.5 g of ethyl 4-[(5,6-dimethyl-8-nitrotetraazolo[1,5-*a*]pyridin-7-yl)amino]butanoate.

Part C

A mixture of ethyl 4-[(5,6-dimethyl-8-nitrotetraazolo[1,5-*a*]pyridin-7-yl)amino]butanoate (10.0 g, 31.0 mmol), 10% palladium on carbon (1.0 g), and acetonitrile (310 mL) was added to a pressure vessel, and the reaction was placed under hydrogen pressure (30 psi, 2.1 x 10^5 Pa) overnight. The reaction mixture was filtered through a layer of CELITE filter agent, and the filter cake was washed with methanol (50 mL). The filtrate was concentrated under reduced pressure to provide ethyl 4-[(8-amino-5,6-dimethyltetraazolo[1,5-*a*]pyridin-7-yl)amino]butanoate as a solid. This reaction was repeated a second time.

Part D

For Examples 40 and 41, pyridine hydrochloride (1.34 g, 11.6 mmol) and trimethyl orthobutyrate (5.42 mL, 34.1 mmol) were sequentially added with stirring to a solution of ethyl 4-[(8-amino-5,6-dimethyltetraazolo[1,5-*a*]pyridin-7-yl)amino]butanoate (9.1 g, 31 mmol) in toluene (310 mL) under a nitrogen atmosphere. The reaction was heated at reflux for 1.5 hours, allowed to cool to ambient temperature overnight, and concentrated under reduced pressure. The residue was partitioned between chloroform (300 mL) and saturated aqueous sodium bicarbonate (75 mL). The aqueous layer was extracted with chloroform (2 x 100 mL), and the combined organic fractions were washed with saturated aqueous sodium bicarbonate (2 x 75 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting solid was triturated with ethyl acetate and isolated by filtration to provide 6.0 g of ethyl 4-(5,6-dimethyl-8-propyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butanoate as a white solid.

For Examples 42 and 43, pyridine hydrochloride (668 mg, 5.78 mmol) and triethyl orthopropionate (3.4 mL, 17 mmol) were added to a solution of ethyl 4-[(8-amino-5,6-dimethyltetraazolo[1,5-*a*]pyridin-7-yl)amino]butanoate (4.5 g, 15 mmol) in toluene (100 mL). The reaction and work-up procedure were as described for Examples 40 and 41. The crude product was recrystallized from ethyl acetate:hexane, isolated by filtration, washed with ethyl acetate:hexane, and dried under high vacuum to provide 4.7 g of ethyl 4-(8-ethyl-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butanoate as off-white crystals.

For Examples 44 and 45, a solution of ethyl 4-[(8-amino-5,6-dimethyltetraazolo[1,5-*a*]pyridin-7-yl)amino]butanoate (4.5 g, 15 mmol) in

dichloromethane (150 mL) was cooled to 0 °C under a nitrogen atmosphere. Ethoxyacetyl chloride (2.46 g, 18.5 mmol) was added dropwise, and the reaction was allowed to warm to ambient temperature and stirred for four hours. Additional ethoxyacetyl chloride (0.5 g) was added, and the reaction was stirred for three days. Additional ethoxyacetyl chloride (1.0 g) was again added, and the reaction was stirred for two hours and concentrated under reduced pressure.

Part E

For Examples 40-43, aqueous sodium hydroxide (2.0 equivalents of 2 M or 6 M) was added dropwise to a suspension of the material from Part D in ethanol (0.2 M) under a nitrogen atmosphere. The reaction was stirred for one hour and concentrated under reduced pressure. The residue was dissolved in a small amount of water (5-8 mL), and the resulting solution was adjusted to pH 4 with the addition of 2 M hydrochloric acid. A precipitate formed and was isolated by filtration, washed with water, and optionally mixed with toluene, which was removed under reduced pressure. The resulting solid was dried under vacuum for two to several hours, optionally at 60-70 °C.

For Examples 44 and 45, aqueous sodium hydroxide (39 mL of 2 M) was added dropwise to a suspension of the material from Part D in ethanol (154 mL), and the reaction was heated at 60 °C under nitrogen for two hours. The reaction was allowed to cool to ambient temperature, adjusted to pH 7 with the addition of 1 N hydrochloric acid, and allowed to stand overnight. The solvent was removed under reduced pressure. Toluene (50 mL) and methanol (10 mL) were twice added and removed under reduced pressure. The residue was dried under high vacuum, mixed with methanol (200 mL), and filtered to remove sodium chloride. The filter cake was washed with methanol, and the filtrate was concentrated under reduced pressure to provide a solid.

Part F

Under a nitrogen atmosphere, oxalyl choride (3.0 equivalents) was added dropwise over a period of five minutes to a suspension of the butanoic acid from Part E in dichloromethane (0.1 M) and four drops of DMF. The reaction was stirred for one hour, and additional oxalyl chloride (0.5 mL) was added in Examples 40, 41, 44, and 45. The solvent was removed under reduced pressure.

Part G

For Examples 40, 42, and 44, a suspension of the acid chloride from Part F in dichloromethane (0.1 M) was cooled to 0 °C under a nitrogen atmosphere. Ammonia (1.5 equivalents of a 0.5 M solution in dioxane) was added dropwise over a period of five minutes. The reaction was stirred for ten minutes, and then ammonia gas was bubbled through the solution for ten minutes. The reaction was stirred overnight at ambient temperature and concentrated under reduced pressure. The residue was triturated with water (Example 40 and 44) or water:ethyl acetate (Example 42), isolated by filtration, washed with water or water:ethyl acetate, and dried under vacuum for two to three hours optionally at 70 °C to provide the amide product as a solid.

For Examples 41, 43, and 45, a suspension of the acid chloride from Part F in dichloromethane (0.1 M) was cooled to 0 °C under a nitrogen atmosphere. Morpholine (6.0 equivalents) was added dropwise over a period of five minutes, and the reaction was stirred overnight at ambient temperature. The solvent was removed under reduced pressure. For Example 41, the residue was triturated with ethyl acetate (30 mL) and methanol (5 mL), and the resulting solid was isolated by filtration, washed with ethyl acetate, and partitioned between chloroform (100 mL) and saturated aqueous sodium bicarbonate (40 mL). The aqueous layer was separated and extracted with chloroform (2 x 50 mL), and the combined organic fractions were washed with saturated aqueous sodium bicarbonate (2 x 30 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide a white solid. For Example 43, the residue was triturated with ethyl acetate:water, and the resulting solid was isolated by filtration, washed with ethyl acetate and water, and dried in a vacuum oven for one hour at 70 °C. For Example 45, the residue was subjected to the aqueous work-up procedure described for Example 41. The resulting solid was triturated with ethyl acetate, isolated by filtration, washed with ethyl acetate, and dried under high vacuum to provide a white solid.

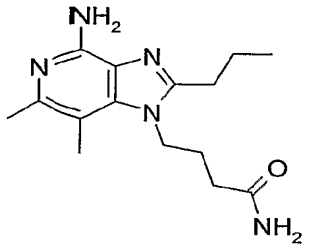
Part H

A pressure vessel was charged with the material from Part G, platinum (IV) oxide (20 wt.%), and trifluoroacetic acid (0.1 M), and the mixture was placed under hydrogen pressure (50 psi, 3.4 x 10^5 Pa) and shaken over three days. The reaction mixture was filtered, optionally through a pad of CELITE filter agent (Example 40), and the filter cake was washed with methanol. The filtrate was concentrated under reduced pressure, and the

residue was mixed with 1 N hydrochloric acid (5-10 mL), stirred for between 1.5 and three hours, cooled to 0 °C, and optionally diluted with chloroform (20-30 mL). The resulting mixture was made basic with the addition of 6 N sodium hydroxide (Examples 40, 42, and 43), 6 N aqueous potassium carbonate (Examples 44 and 45), or saturated aqueous sodium bicarbonate (Example 41). For Examples 40 and 42, a precipitate formed, was isolated by filtration, dissolved in methanol, and concentrated under reduced pressure. For Examples 41 and 43-45, the aqueous layer was separated and extracted with chloroform (3 x 50 mL). The combined organic fractions were washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The purification and characterization is given below for each product.

Example 40

4-(4-Amino-6,7-dimethyl-2-propyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butanamide

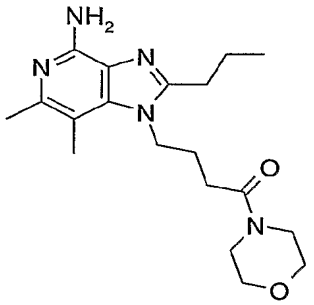


The product was triturated with ethyl acetate, isolated by filtration, triturated with methanol, isolated by filtration, washed with methanol and acetonitrile, and dried overnight under high vacuum at 80 °C to provide 4-(4-amino-6,7-dimethyl-2-propyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butanamide as a white powder, mp 226.0-228.0 °C.

Anal. Calcd for $C_{15}H_{23}N_5O$: C, 62.26; H, 8.01; N, 24.20; Found: C, 61.99; H, 8.07; N, 24.36.

Example 41

6,7-Dimethyl-1-(4-morpholin-4-yl-4-oxobutyl)-2-propyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine

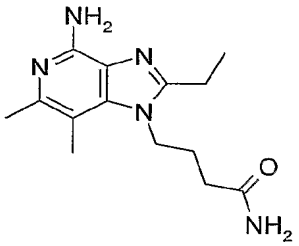


The product was purified by chromatography using a HORIZON HPFC system (eluting with chloroform:CMA in a gradient from 95:5 to 60:40) followed by recrystallization from ethyl acetate. The crystals were dried under high vacuum to provide 6,7-dimethyl-1-(4-morpholin-4-yl-4-oxobutyl)-2-propyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine as a white powder, mp 164.0-165.0 °C.

Anal. Calcd for $C_{19}H_{29}N_5O_2$: C, 63.48; H, 8.13; N, 19.48. Found: C, 63.30; H, 8.33; N, 19.49.

Example 42

4-(4-Amino-2-ethyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butanamide

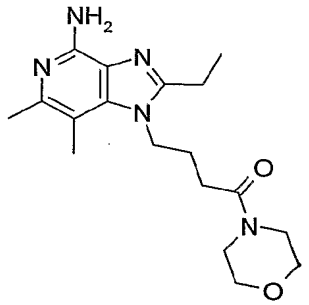


The product was triturated with acetonitrile, isolated by filtration, triturated with 1 N sodium hydroxide, isolated by filtration, washed with water, triturated with ethyl acetate, and dried under high vacuum with stirring at 100 °C for three hours to provide 4-(4-amino-2-ethyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butanamide as a white powder, mp 228.0-230.0 °C.

Anal. Calcd for $C_{14}H_{21}N_5O \cdot 0.09H_2O$: C, 60.71; H, 7.71; N, 25.29. Found: C, 60.45; H, 8.07; N, 25.56.

Example 43

2-Ethyl-6,7-dimethyl-1-(4-morpholin-4-yl-4-oxobutyl)-1*H*-imidazo[4,5-*c*]pyridin-4-amine

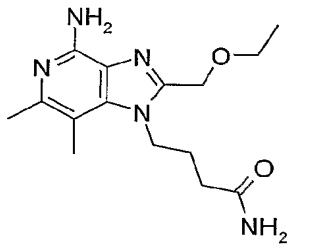


The product was triturated with ethyl acetate, dried under high vacuum, recrystallized twice from acetonitrile, isolated by filtration, washed with acetonitrile, and dried under high vacuum with stirring at 100 °C for three hours to provide 2-ethyl-6,7-dimethyl-1-(4-morpholin-4-yl-4-oxobutyl)-1*H*-imidazo[4,5-*c*]pyridin-4-amine as a white powder, mp 209.0-210.0 °C.

Anal. Calcd for $C_{18}H_{27}N_5O_2$: C, 62.59; H, 7.88; N, 20.27. Found: C, 62.49; H, 8.09; N, 20.34.

Example 44

4-[4-Amino-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butanamide

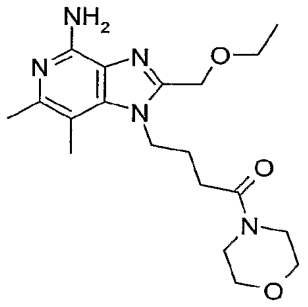


The product was triturated with ethyl acetate, isolated by filtration, washed with ethyl acetate, sonicated with 1 N sodium hydroxide for one minute, isolated by filtration, washed with water, and dried under high vacuum overnight to provide 4-[4-amino-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butanamide as a white powder, mp 199.0-200.0 °C.

Anal. Calcd for $C_{15}H_{23}N_5O_2$: C, 59.00; H, 7.59; N, 22.93. Found: C, 58.72; H, 7.53; N, 22.76.

Example 45

2-(Ethoxymethyl)-6,7-dimethyl-1-(4-morpholin-4-yl-4-oxobutyl)-1*H*-imidazo[4,5-*c*]pyridin-4-amine

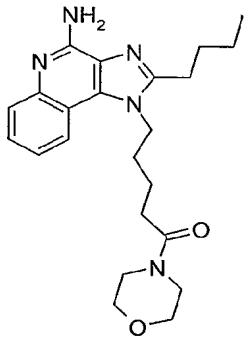


The product was triturated with ethyl acetate, isolated by filtration, washed with ethyl acetate, sonicated with 1 N sodium hydroxide (5 mL) for 30 seconds, and diluted with water (20 mL) and chloroform (50 mL). The aqueous layer was separated and extracted with chloroform (3 x 20 mL). The combined organic fractions were washed with 1 N sodium hydroxide (10 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was triturated with ethyl acetate, isolated by filtration, and dried under high vacuum for two hours at 70 °C to provide 2-(ethoxymethyl)-6,7-dimethyl-1-(4-morpholin-4-yl-4-oxobutyl)-1*H*-imidazo[4,5-*c*]pyridin-4-amine as a white powder, mp 156.0-158.0 °C.

Anal. Calcd for $C_{19}H_{29}N_5O_3$: C, 60.78; H, 7.785; N, 18.65. Found: C, 60.44; H, 8.07; N, 18.32.

Example 46

2-Butyl-1-(5-morpholin-4-yl-5-oxopentyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine

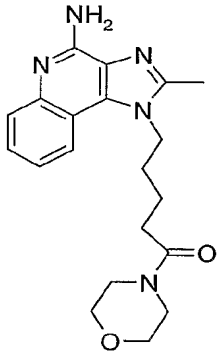


The methods described in Parts C, D, E, and F of Example 34 were used to treat ethyl 5-(3-aminoquinolin-4-ylamino)pentanoate, prepared in Parts A and B of Example 34. Trimethyl orthovalerate was used instead of trimethyl orthobutyrate in Part C. Following chromatographic purification of the product from Part F (eluting with 95:5 dichloromethane:methanol), 2-butyl-1-(5-morpholin-4-yl-5 -oxopentyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine was obtained as an off-white powder, mp 141-143 °C.

Anal. Calcd for $C_{23}H_{31}N_5O_2$: C, 67.46; H, 7.63; N, 17.10. Found: C, 67.37; H, 7.66; N, 16.90.

Example 47

2-Methyl-1-(5-morpholin-4-yl-5-oxopentyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

The methods described in Parts C, D, and E of Example 34 were used to convert 5 ethyl 5-(3-aminoquinolin-4-ylamino)pentanoate, prepared in Parts A and B of Example 34, to 2-methyl-1-(5-morpholin-4-yl-5-oxopentyl)-1*H*-imidazo[4,5-*c*]quinoline. Trimethyl

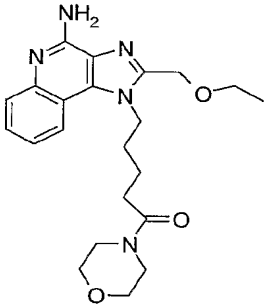
orthoacetate was used instead of trimethyl orthobutyrate in Part C, and the reaction was heated for four hours. In Part E, the treatment with oxalyl chloride (1.8 equivalents) was carried out three times for 15 minutes each time. DMF (5 mL) was added to the reaction before the first addition.

Part B

2-Methyl-1-(5-morpholin-4-yl-5-oxopentyl)-1*H*-imidazo[4,5-*c*]quinoline (8.4 g, 24 mmol) was treated with mCPBA (7.19 g, 41.7 mmol), ammonium hydroxide (40 mL), and benzenesulfonyl chloride (5.93 mL, 46.5 mmol) according to the method described in Part D of Example 36. The crude product was purified by column chromatography on silica gel (eluting with 90:10 dichloromethane:methanol). The resulting product was triturated with 10% aqueous sodium hydroxide, isolated by filtration, washed with water, and dried overnight in a vacuum oven to provide 0.487 g of 2-methyl-1-(5-morpholin-4-yl-5-oxopentyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as an off-white powder, mp 218-219 °C. Anal. Calcd for $C_{20}H_{25}N_5O_2$: C, 65.37; H, 6.86; N, 19.06. Found: C, 65.20; H, 7.03; N, 18.98.

Example 48

2-(Ethoxymethyl)-1-(5-morpholin-4-yl-5-oxopentyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



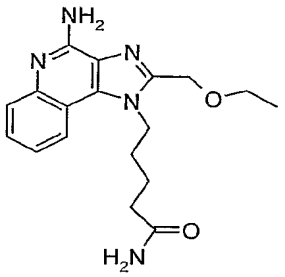
The methods described in Parts A through D of Example 36 were used to treat ethyl 5-(3-aminoquinolin-4-ylamino)pentanoate, prepared in Parts A and B of Example 34. Ethoxyacetyl chloride was used instead of methoxypropionyl chloride in Part A. Following chromatographic purification of the product from Part D (eluting with 95:5 dichloromethane:methanol), the product was triturated with 10% sodium hydroxide, isolated by filtration, washed with water, and dried overnight in a vacuum oven to provide

2-(ethoxymethyl)-1-(5-morpholin-4-yl-5-oxopentyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a tan solid, mp 128-129 °C.

Anal. Calcd for $C_{22}H_{29}N_5O_3 \cdot 0.54H_2O$: C, 62.72; H, 7.20; N, 16.62. Found: C, 62.72; H, 7.16; N, 16.60.

Example 49

5-[4-Amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]pentanamide



Part A

Ethyl 5-(3-aminoquinolin-4-ylamino)pentanoate, prepared in Parts A and B of Example 34, was treated as described in Part A of Example 36. Ethoxyacetyl chloride was used instead of methoxypropionyl chloride. Ethyl 5-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanoate (6.0 g, 17 mmol) and ammonium acetate (15 g) were sealed in a high-pressure vessel and heated for four days at 110 °C and then allowed to cool to ambient temperature. Aqueous sodium hydroxide (10%) was added, and the mixture was then extracted with dichloromethane (3 x). The product crystallized from the dichloromethane and was collected in two crops to provide 2.64 g of 5-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]pentanamide as an off-white solid, mp 157-158 °C.

Anal. Calcd for $C_{18}H_{22}N_4O_2$: C, 66.24; H, 6.79; N, 17.17. Found: C, 65.99; H, 6.67; N, 17.08.

Part B

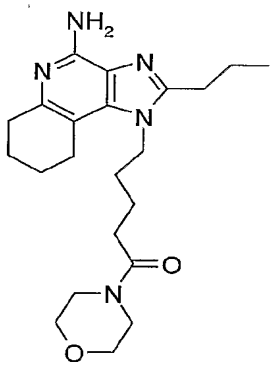
5-[2-(Ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]pentanamide (2.25 g, 6.89 mmol) was treated with mCPBA (2.77 g, 12.0 mmol), ammonium hydroxide (40 mL), and benzenesulfonyl chloride (1.71 mL, 13.4 mmol) according to the method described in Part D of Example 36. The crude product was purified by column chromatography on silica gel (eluting with dichloromethane:methanol in a gradient from 90:10 to 85:15). The resulting product was triturated with 10% aqueous sodium hydroxide, isolated by

filtration, washed with water, and dried overnight in a vacuum oven to provide 0.752 g of 5-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]pentanamide as a tan solid, mp 198-200 °C.

Anal. Calcd for $C_{18}H_{23}N_5O_2 \cdot 0.21\ H_2O$: C, 62.64; H, 6.84; N, 20.29. Found: C, 62.26; H, 6.80; N, 19.96.

Example 50

1-(5-Morpholin-4-yl-5-oxopentyl)-2-propyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine

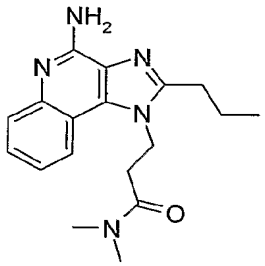


A mixture of 1-(5-morpholin-4-yl-5-oxopentyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (1.66 g, 4.19 mmol, prepared in Example 34), platinum (IV) oxide (1.5 g, 6.6 mmol), and trifluoroacetic acid (25 mL) was placed in a Parr vessel and shaken under hydrogen pressure (40 psi, 2.8 x 10^5 Pa) overnight. The reaction mixture was filtered through a layer of CELITE filter agent, and the filter cake was washed with ethanol. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (eluting with 95:5 dichloromethane:methanol). The resulting solid was triturated three times with 10% aqueous sodium hydroxide, isolated by filtration, and washed with water to provide 0.468 g of 1-(5-morpholin-4-yl-5-oxopentyl)-2-propyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 158-160 °C.

Anal. Calcd for $C_{22}H_{33}N_5O_2 \cdot 0.05\ H_2O$: C, 65.99; H, 8.33; N, 17.49. Found: C, 65.59; H, 8.60; N, 17.76.

Example 51

3-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*,*N*-dimethylpropanamide



Part A

Dimethylamine (15 mL of a 40% aqueous solution) was added to a solution of ethyl 3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanoate (4.02 g, 12.9 mmol, prepared in Part B of Example 18) in THF (7 mL), and the reaction mixture was heated at 110 °C overnight in a pressure vessel. The reaction was allowed to cool to ambient temperature and concentrated under reduced pressure to provide 4.1 g of *N*,*N*-dimethyl-3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanamide as a dark brown solid.

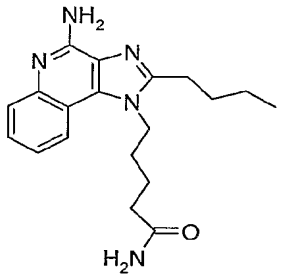
Part B

N,*N*-Dimethyl-3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanamide (2.40 g, 7.73 mmol) was treated with mCPBA (3.11 g, 13.5 mmol), ammonium hydroxide (40 mL), and benzenesulfonyl chloride (1.92 mL, 15.1 mmol) according to the method described in Part D of Example 36. The crude product was purified by column chromatography on silica gel (eluting with 93:7 dichloromethane:methanol) to provide 0.097 g of 3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*,*N*-dimethylpropanamide as a tan powder, mp 207-209 °C.

Anal. Calcd for $C_{18}H_{23}N_5O \cdot 0.19\ H_2O$: C, 65.75; H, 7.07; N, 21.3. Found: C, 65.71; H, 7.38; N, 20.9.

Example 52

5-(4-Amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanamide



Part A

Ethyl 5-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanoate (10.0 g, 28.2 mmol, prepared in Example 46) and ammonium acetate (10 g) were sealed in a high-pressure vessel, heated for two days at 130 °C, and then allowed to cool to ambient temperature. Saturated aqueous sodium bicarbonate was added, and the mixture was then extracted with dichloromethane. The combined organic fractions were washed sequentially with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 8.6 g of 5-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanamide.

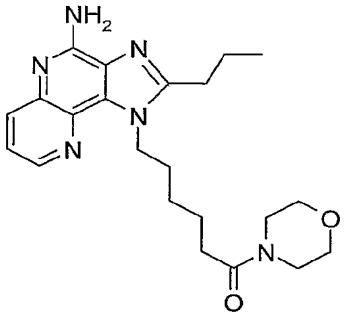
Part B

5-(2-Butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanamide (8.6 g, 26.5 mmol) was treated with mCPBA (10.7 g, 46.4 mmol), ammonium hydroxide (40 mL), and benzenesulfonyl chloride (6.59 mL, 51.6 mmol) according to the method described in Part D of Example 36. The crude product was purified by column chromatography on silica gel (eluting with dichloromethane:methanol in a gradient from 90:10 to 80:20). The resulting product was sonicated three times with 10% aqueous sodium hydroxide and once with 30% aqueous sodium hydroxide, isolated by filtration, washed with water, and dried overnight in a vacuum oven to provide 0.367 g of 5-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanamide as a tan solid, mp 219-221 °C.

Anal. Calcd for $C_{19}H_{25}N_5O \cdot 0.21\ H_2O$: C, 66.50; H, 7.46; N, 20.41. Found: C, 66.34; H, 7.81; N, 20.01.

Example 53

1-(6-Morpholin-4-yl-6-oxohexyl)-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine



Part A

A suspension of 4-chloro-3-nitro[1,5]naphthyridine (9.0 g, 42.9 mmol) in chloroform (180 mL) was cooled to approximately 0 °C. Ethyl 6-aminohexanoate hydrochloride (12.6 g, 64.4 mmol) and triethylamine (16.6 mL, 119 mmol) were sequentially added with stirring, and the reaction was stirred for 15 minutes. The mixture was diluted with chloroform (180 mL), washed with 1% aqueous sodium carbonate (3 x 125 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide ethyl 6-(3-nitro[1,5]naphthyridin-4-ylamino)hexanoate as a yellow oil.

Part B

The method described in Part B of Example 37 was used to hydrogenate the material from Part A to provide 6-(3-amino[1,5]naphthyridin-4-ylamino) ethyl hexanoate, which was dissolved in chloroform (650 mL) and divided into three portions (300 mL, 175 mL, and 175 mL).

Part C

Butyryl chloride (3.61 mL, 34.7 mmol) was added in four portions over the course of 105 minutes to a 175 mL portion from Part B. After a total reaction time of two hours, the solvent was removed under reduced pressure. The residue was triturated with acetone (2 mL/g) while cooling to approximately 0 °C, and the resulting solid was isolated by filtration, air-dried, and suspended in ethanol (33 mL). A mixture of 50 % (w/w) aqueous sodium hydroxide (2.78 g, 34.7 mmol) and 11.4 mL water was added with stirring, and the resulting mixture was stirred at ambient temperature for ten minutes, heated at 85 °C for one hour, and allowed to cool to ambient temperature. The solvents were removed under reduced pressure, and the residue was partitioned between chloroform (90 mL) and

deionized water (15 mL) and stirred for ten minutes. The aqueous phase was adjusted to pH 5 with the addition of 1 N hydrochloric acid, and then the organic phase was separated, dried over sodium sulfate, and concentrated under reduced pressure to provide 3.8 g of 6-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]hexanoic acid.

Part D

A solution of oxalyl chloride (2.04 mL, 23.4 mmol) in dichloromethane (15 mL) was added dropwise to a suspension of 6-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]hexanoic acid (2.56 g, 7.8 mmol) in dichloromethane (38 mL) containing one drop of DMF. The reaction mixture was stirred at ambient temperature for 1.75 hours, and then additional oxalyl chloride (0.35 mL, 4.1 mmol) was added. The reaction was stirred for an additional 45 minutes and then concentrated under reduced pressure to provide 6-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]hexanoyl chloride.

Part E

Morpholine (1.72 mL, 19.6 mmol) was added to a solution of the material from Part D in dichloromethane (20 mL/g), and the reaction was stirred for 30 minutes at ambient temperature and then diluted with dichloromethane (20 mL/g) and saturated aqueous sodium bicarbonate (20 mL/g). The organic fraction was separated and concentrated under reduced pressure to provide 1-(6-morpholin-4-yl-6-oxohexyl)-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridine.

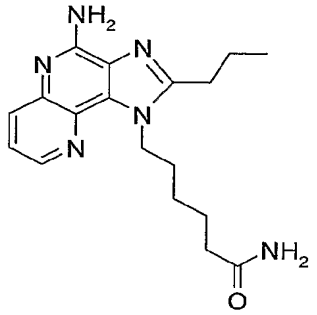
Part F

mCPBA (70-77% purity, 4.52 g) was added to a solution of the material from Part E in chloroform (40 mL), and the reaction was stirred for 3.25 hours before the addition of more mCPBA (2.26 g). The stirring was continued for an additional 45 minutes, and then the reaction was diluted with chloroform (30 mL/g), washed twice with 1% aqueous sodium carbonate, and concentrated under reduced pressure. The residue was dissolved in dichloromethane (25 mL), and ammonium hydroxide (13 mL of 28%) and *p*-toluenesulfonyl chloride (1.93 g, 10.1 mmol) were sequentially added. The reaction mixture was stirred for 15 minutes, and additional dichloromethane (75 mL) was added. The organic layer was separated, dried over sodium sulfate, and concentrated under reduced pressure. The crude product (5.06 g) was purified by column chromatography on silica gel (eluting with 2.5% methanol in chloroform) followed by recrystallization from acetonitrile/water. The crystals were dried in a vacuum oven for three days at 90 °C and

for four hours at 112 °C to provide 1.25 g of 1-(6-morpholin-4-yl-6-oxohexyl)-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine as a light yellow solid, mp 148-150 °C. Anal. calcd for $C_{22}H_{30}N_6O_2$: C, 64.37; H, 7.37; N, 20.47. Found: C, 64.19; H, 7.58; N, 20.70.

Example 54

6-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)hexanamide



Part A

A solution of 6-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]hexanoyl chloride, prepared according to the methods described in Parts A through D of Example 53, (4.8 mmol) in dichloromethane (20 mL/g) was cooled to approximately 0 °C, and anhydrous ammonia was bubbled through the solution for ten minutes. The reaction was warmed to ambient temperature and stirred for an additional 30 minutes. Chloroform (20 mL/g) and water (15 mL/g) were added to the reaction. The aqueous layer was separated and extracted with dichloromethane (20 mL). The combined organic fractions were concentrated under reduced pressure. The crude product was recrystallized from acetonitrile (19 mL/g) to provide 1.20 g of 6-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)hexanamide.

Part B

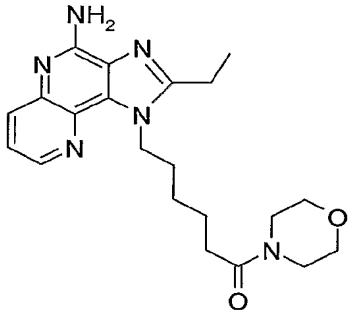
A modification of the method described in Part F of Example 53 was used to treat 6-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)hexanamide (1.20 g, 3.7 mmol) with mCPBA (2.47 g of 70-77% purity) followed by ammonium hydroxide (4 mL), and *p*-toluenesulfonyl chloride (0.70 g). After the amination reaction was stirred for one hour, a precipitate was present and was isolated by filtration and washed with chloroform and water. The precipitate was ground up and dried for three days at 70 °C and then overnight

at 95 °C to provide 0.46 g of 6-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)hexanamide as a white solid, mp 216.5-217.5 °C.

Anal. calcd for $C_{18}H_{24}N_6O$: C, 63.51; H, 7.11; N, 24.69. Found: C, 63.29; H, 7.10; N, 24.68.

Example 55

2-Ethyl-1-(6-morpholin-4-yl-6-oxohexyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine



Part A

Propionyl chloride (5.17 mL, 59.5 mmol) was added in three portions (19.8 mmol each) 45 to 60 minutes apart to the 300 mL portion from Part B of Example 53. After a total reaction time of three hours, the solvent was removed under reduced pressure. The residue was purified, isolated, and treated with a mixture of 50 % (w/w) aqueous sodium hydroxide (4.76 g, 59.6 mmol) and 18.8 mL water according to the methods described in Part C of Example 53. The methods of Part C of Example 53 were then used to isolate 3.56 g of 6-(2-ethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]hexanoic acid.

Part D

The method described in Part D of Example 53 was used to treat 6-(2-ethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]hexanoic acid (3.46 g, 11.1 mmol) with oxalyl chloride (3.87 mL, 44.0 mmol) to obtain 6-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]hexanoyl chloride, which was dissolved in dichloromethane (20 mL/g) and divided into two equal portions.

Part E

Morpholine (1.21 mL, 13.8 mmol) was added to one portion from Part D, and the reaction was stirred for 15 minutes at ambient temperature and then diluted with dichloromethane (20 mL/g) and saturated aqueous sodium bicarbonate (20 mL/g). The

organic fraction was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide 2-ethyl-1-(6-morpholin-4-yl-6-oxohexyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine.

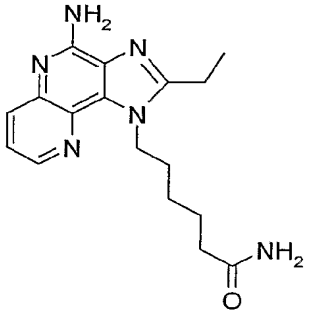
Part F

The method described in Part F of Example 53 was used to treat the material from Part E with mCPBA (4.92 g of 70-77% purity) followed by ammonium hydroxide (9 mL) and *p*-toluenesulfonyl chloride (1.40 g, 7.34 mmol). The crude product (3.22 g) was purified by column chromatography on silica gel (eluting with 2.5% methanol in chloroform) followed by recrystallization from acetonitrile. The crystals were dried in a vacuum oven for three days at 90 °C and for four hours at 112 °C to provide 0.79 g of 2-ethyl-1-(6-morpholin-4-yl-6-oxohexyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine as a light yellow solid, mp 163-165 °C.

Anal. calcd for $C_{21}H_{28}N_6O_2$: C, 63.61; H, 7.12; N, 21.20. Found: C, 63.52; H, 7.29; N, 21.47.

Example 56

6-(4-Amino-2-ethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)hexanamide



Part A

The second portion of the solution from Part D of Example 55 was cooled to approximately 0 °C, and anhydrous ammonia was bubbled through the solution for ten minutes. The reaction was warmed to ambient temperature and stirred for an additional 30 minutes. Chloroform (30 mL/g) and water (15 mL/g) were added to the reaction, and the mixture was stirred for 30 minutes. The organic fraction was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was

recrystallized from acetonitrile (10 mL/g) to provide 1.18 g of 6-(2-ethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)hexanamide.

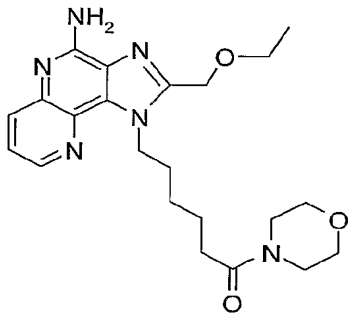
Part B

A modification of the method described in Part F of Example 53 was used to treat 6-(2-ethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)hexanamide (1.18 g, 3.8 mmol) with mCPBA (2.54 g of 70-77% purity) followed by ammonium hydroxide (4 mL), and *p*-toluenesulfonyl chloride (0.72 g). After the amination reaction was stirred for 15 minutes, a precipitate was present and was isolated by filtration. The precipitate was purified by chromatography using a HORIZON HFPC system (silica cartridge, eluting with 0-55% CMA in chloroform) and dried for three days at 90 °C to provide 0.34 g of 6-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)hexanamide as a light yellow solid, mp 220-221 °C.

Anal. calcd for $C_{17}H_{24}N_6O_2 \cdot 0.1\ H_2O$: C, 62.21; H, 6.82; N, 25.61. Found: C, 61.69; H, 6.89; N, 25.54.

Example 57

2-(Ethoxymethyl)-1-(6-morpholin-4-yl-6-oxohexyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine



Part A

Ethoxyacetyl chloride (1.55 g, 12.2 mmol) was added to a 175 mL portion of the solution from Part B of Example 53. After a total reaction time of one hour, the solvent was removed under reduced pressure. The residue was triturated with ethyl acetate (2 mL/g) while cooling to approximately 0 °C, and the resulting solid was isolated by filtration, air-dried, and treated with a mixture of 50 % (w/w) aqueous sodium hydroxide (2.78 g, 34.7 mmol) and 11.8 mL water according to the method described in Part C of

Example 53. A solid was present during the work-up between the organic and acidic aqueous phases. The solid was isolated by filtration, triturated with methanol, isolated by filtration, dried under reduced pressure, and combined with the material isolated from the organic phase to provide 3.25 g of 6-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]hexanoic acid.

Part B

The method described in Part D of Example 53 was used to treat 6-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]hexanoic acid (3.23 g, 9.4 mmol) with oxalyl chloride (3.29 mL, 37.7 mmol) to obtain 6-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]hexanoyl chloride. The reaction was complete in two hours.

Part C

The method described in Part E of Example 53 was used to treat the material from Part B with morpholine (2.06 mL, 23.6 mmol) to provide 2-(ethoxymethyl)-1-(6-morpholin-4-yl-6-oxohexyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine.

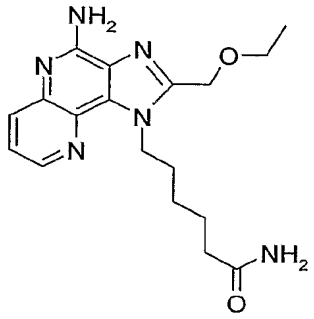
Part D

The method described in Part F of Example 53 was used to treat the material from Part C with mCPBA (8.15 g of 70-77% purity) followed by ammonium hydroxide (15 mL) and *p*-toluenesulfonyl chloride (2.32 g). The crude product (5.91 g) was purified by column chromatography on silica gel (eluting with 2% methanol in chloroform) followed by recrystallization from acetonitrile/water. The crystals were dried in a vacuum oven for three days at 90 °C and for four hours at 112 °C to provide 0.63 g of 2-(ethoxymethyl)-1-(6-morpholin-4-yl-6-oxohexyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine as a light yellow solid, mp 168-170 °C.

Anal. calcd for $C_{22}H_{30}N_6O_3$: C, 61.95; H, 7.09; N, 19.70. Found: C, 61.80; H, 7.13; N, 19.96.

Example 58

6-[4-Amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]hexanamide



Part A

A solution of 6-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]hexanoyl chloride, prepared according to the methods described in Parts A and B of Example 57, (5.8 mmol) in dichloromethane (20 mL/g) was cooled to approximately 0 °C, and anhydrous ammonia was bubbled through the solution for ten minutes. The reaction was warmed to ambient temperature and stirred for an additional 30 minutes. Chloroform (20 mL/g) and water (15 mL/g) were added to the reaction. A solid was present and was isolated by filtration to provide 0.96 g of 6-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]hexanamide. The filtrate was concentrated under reduced pressure, and the residue was partitioned between chloroform (75 mL) and 1% aqueous sodium carbonate (20 mL). The organic fraction was concentrated under reduced pressure, and the residue was triturated with acetonitrile and isolated by filtration to provide an additional 0.74 g of product. The two solids were combined and used in the next step.

Part B

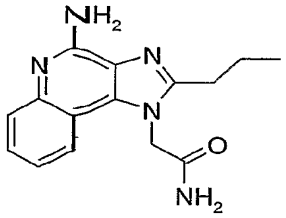
A modification of the methods described in Part F of Example 53 was used to treat 6-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)hexanamide (1.70 g, 5.0 mmol) with mCPBA (3.34 g of 70-77% purity) followed by ammonium hydroxide (5.5 mL), and *p*-toluenesulfonyl chloride (0.95 g). After the amination reaction was stirred for one hour, a precipitate was present and was isolated by filtration and washed with chloroform and water. The precipitate was triturated with 2-propanol (7.5 mL/g at 97 °C), and the mixture was filtered hot. The isolated solid was dried overnight under vacuum and then in a vacuum oven for six days at 65 °C. The product was then sonicated in 1 M

aqueous sodium hydroxide for 15 minutes, isolated by filtration, washed with deionized water, and dried in a vacuum oven for three days at 90 °C to provide 0.32 g of 6-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]hexanamide as a yellow solid, mp 215-217 °C.

Anal. calcd for $C_{18}H_{24}N_6O_2 \cdot 0.37\ H_2O$: C, 59.54; H, 6.87; N, 23.15. Found: C, 59.66; H, 7.00; N, 23.44.

Example 59

2-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)acetamide



Part A

Triethylamine (22.3 mL, 0.160 mol) was added with stirring to a solution of 3-amino-4-chloroquinoline, see Surrey et al., *Journal of the American Chemical Society*, 73, pp. 2413-2416 (1951), (13.2 g, 74.0 mmol) in anhydrous dichloromethane (100 mL). A solution of butyryl chloride (13 mL, 125 mmol) in dichloromethane (50 mL) was then added dropwise, and the reaction mixture was stirred at ambient temperature overnight. Methanol (25 mL) was added, and the reaction mixture was stirred for one hour at ambient temperature. Saturated aqueous sodium bicarbonate (50 mL) was added, and the resulting mixture was stirred at ambient temperature for 30 minutes and then allowed to stand. The aqueous layer was separated and extracted with dichloromethane (75 mL), and the combined organic fractions were then washed with saturated aqueous sodium bicarbonate (2 x 50 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure. The crude product (22.8 g) was recrystallized from a mixture of toluene (45 mL) and hexane (15 mL) to provide 9.2 of *N*-(4-chloroquinolin-3-yl)butanamide as brown needles.

Part B

A neat mixture of *N*-(4-chloroquinolin-3-yl)butanamide (5.0 g, 20 mmol) and glycine ethyl ester hydrochloride (10.0 g, 72 mmol) was heated gently with a heat gun

until the solids melted. The reaction was followed by LC/MS, and heat was applied briefly twice more until no starting material remained. Dichloromethane (100 mL) and saturated aqueous sodium bicarbonate (50 mL) were added, and the resulting mixture was stirred until all solids were dissolved. The aqueous layer was separated and extracted with dichloromethane (2 x 50 mL), and the combined organic fractions were washed sequentially with saturated aqueous sodium bicarbonate (50 mL) and water, dried over potassium carbonate, filtered, and concentrated under reduced pressure. The residue was (3.6 g) was dissolved in hot toluene (150 mL), and pyridinium tosylate (100 mg) was added. The reaction was heated at reflux under a Dean–Stark trap for one hour, allowed to stand at ambient temperature for three days, heated at reflux for two hours, cooled to ambient temperature, and diluted with dichloromethane (150 mL). The resulting solution was washed with saturated aqueous sodium bicarbonate (2 x 35 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide 3.2 g of ethyl (2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)acetate as a light brown solid.

Part C

mCPBA (4.70 g of 75%, 27.3 mmol) was added over a period of five minutes to a solution of ethyl (2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)acetate (3.2 g, 11 mmol) in dichloromethane (100 mL), which had been cooled to approximately 0 °C. The reaction mixture was stirred cold for ten minutes and then for one hour at room temperature at which time analysis by LC/MS indicated that the reaction was not complete. The reaction mixture was stirred for one hour and was still incomplete; additional mCPBA (1.0 g) was added. The reaction was stirred for an additional 30 minutes, and then the aqueous layer was separated and extracted with dichloromethane (2 x 35 mL). The combined organics were washed twice with a mixture of saturated aqueous sodium bicarbonate (33 mL) and 25% aqueous sodium hydroxide (2 mL) and then cooled to 0 °C. With vigorous stirring, ammonium hydroxide (50 mL) was added, and a solution of benzenesulfonyl chloride (2.4 mL, 19 mmol) in dichloromethane (15 mL) was then added dropwise. The reaction mixture was stirred for 15 minutes, warmed to ambient temperature, and then stirred for two hours. The aqueous layer was separated and extracted with dichloromethane (2 x 35 mL). The combined organics were washed twice with a mixture of saturated aqueous sodium bicarbonate (33 mL) and 25% aqueous sodium hydroxide (2 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure. The residue was

purified by column chromatography (silica gel, eluting with 5% methanol in dichloromethane containing 3 mL of ammonium hydroxide per liter of eluent) followed by recrystallization three times from ethanol/water. The crystals were dried in a vacuum oven overnight at 70 °C to provide ethyl (4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)acetate as tan needles, mp 170-172 °C. Anal. calcd for $C_{17}H_{20}N_4O_2 \cdot 0.27\ H_2O \cdot 0.14\ C_2H_5OH$: C, 64.17; H, 6.61; N, 17.33. Found: C, 63.93; H, 6.60; N, 17.10.

Part D

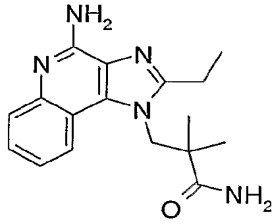
Ethyl (4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)acetate (0.80 g), a solution of ammonia in methanol (35 mL of 7 N), and ammonium chloride (0.50 g) were heated in a sealed pressure vessel at 150 °C for 20 hours. The volatiles were removed under reduced pressure, and the solid residue was triturated with saturated aqueous sodium bicarbonate for one hour, isolated by filtration, and washed with water. The solid was recrystallized from methanol/water, and the crystals were washed sequentially with 25% aqueous sodium hydroxide (2 x 25 mL) and water (2 x 25 mL) and dried overnight in a vacuum oven at 70 °C to provide 0.120 g of 2-(4-amino-2-propyl-1H-imidazo[4,5-c]quinolin-1-yl)acetamide as light tan crystals, mp >300 °C.

MS (APCI) *m/z* 284 ($M + H^+$);

Anal. calcd for $C_{15}H_{17}N_5O$: C, 63.59; H, 6.05; N, 24.72. Found: C, 63.29; H, 5.88; N, 25.07.

Example 60

3-(4-Amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanamide



Part A

Ethyl 3-[(3-aminoquinolin-4-yl)amino]-2,2-dimethylpropanoate (see Example 26 Parts A through D, 3.6 g, 12 mmol) was treated according to a modification of the method described in Part B of Example 8 using triethyl orthopropionate in lieu of trimethyl orthobutyrate. Prior to the addition of triethyl orthopropionate (4.0 mL, 20 mmol) and

pyridinium *p*-toluenesulfonate (0.030 g), the reaction was heated at reflux for 15 minutes. After the reaction was heated at reflux for three hours, it was concentrated under reduced pressure and found to be incomplete by ^{1}H NMR. The oil was dissolved in toluene (100 mL), and concentrated sulfuric acid (one drop) was added. The reaction was heated at reflux for two hours and allowed to cool. Triethylamine (5 mL) was added, and the reaction was heated at reflux for two hours, allowed to cool to ambient temperature, washed with saturated aqueous sodium bicarbonate (2 x 35 mL), dried over potassium carbonate, filtered, and concentrated to provide 3.6 g of ethyl 3-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanoate as an oil.

Part B

mCPBA (4.8 g of 75%, 22 mmol) was added over a period of several minutes to a solution of ethyl 3-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanoate (3.6 g, 11 mmol) in dichloromethane (100 mL), which had been cooled to approximately 0 °C. The reaction mixture was stirred cold for ten minutes and then for three hours at ambient temperature. The reaction mixture was then washed twice with a mixture of saturated aqueous sodium bicarbonate (34 mL) and 25% aqueous sodium hydroxide (1 mL), dried over potassium carbonate, filtered, and then cooled to 0 °C. Trichloroacetyl isocyanate (1.7 mL, 14 mmol) was added, and the reaction was stirred cold for 15 minutes, warmed to ambient temperature, and stirred for one hour. The solvent was removed under reduced pressure, and the residue was dissolved in methanol (50 mL). Sodium methoxide (6.5 mL of a 25% solution in methanol, 30 mmol) was added to the resulting solution, and the reaction was stirred at ambient temperature overnight and cooled to approximately 0 °C for 30 minutes. A precipitate formed and was isolated by filtration to provide 1.2 g of methyl 3-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanoate.

Part C

A solution of potassium hydroxide (16 mL of a 0.5 M solution in methanol) was added to methyl 3-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanoate (1.2 g, 3.7 mmol), and the resulting solution was heated at reflux for five days and allowed to cool to ambient temperature. Hydrogen chloride (8.5 mL of a 1 N solution in diethyl ether) was added, and the reaction was stirred for 30 minutes. The solvents were removed under reduced pressure, and the residue was dissolved in dichloromethane (50 mL). A solution of oxalyl chloride (0.70 mL, 8.0 mmol) in

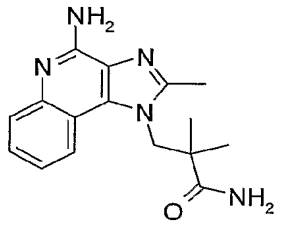
dichloromethane (5 mL) was added, and the solution was stirred overnight at ambient temperature and then concentrated under reduced pressure. The residue was dissolved in dichloromethane (50 mL), and ammonia (10 mL of a 0.5 M solution in 1,4-dioxane) was added. The reaction was stirred for 15 minutes, and then additional ammonia (10 mL of a 7 N solution in methanol) was added. The reaction was stirred for two hours and concentrated under reduced pressure. The residue was stirred with dichloromethane for five minutes, isolated by filtration, and recrystallized from methanol/water. The resulting needles were dried overnight in a vacuum oven at 80 °C to provide 3-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanamide as light yellow needles, mp 279-281 °C.

MS (APCI) *m/z* 312 ($M + H^+$);

Anal. calcd for $C_{17}H_{21}N_5O$: C, 64.35; H, 6.88; N, 22.07. Found: C, 64.14; H, 7.22; N, 22.46.

Example 61

3-(4-Amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanamide



Part A

Ethyl 3-[(3-aminoquinolin-4-yl)amino]-2,2-dimethylpropanoate (see Example 26 Parts A through D, 6.3 g, 2 mmol) was treated according to a modification of the method described in Part B of Example 8 using trimethyl orthoacetate in lieu of trimethyl orthobutyrate. Prior to the addition of trimethyl orthoacetate (3.8 mL, 30 mmol) and pyridinium *p*-toluenesulfonate (0.050 g), the reaction was heated at reflux for 15 minutes. During the work-up procedure, the solution was washed with saturated aqueous sodium bicarbonate (2 x 35 mL) and dried over potassium carbonate. The product, ethyl 2,2-dimethyl-3-(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanoate (7.3 g), was used without purification.

Part B

The methods described in Part B of Example 60 were used to treat ethyl 2,2-dimethyl-3-(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propanoate (7.2 g, 22 mmol) with mCPBA (9.6 g of 77% pure material), followed by trichloroacetyl isocyanate (3. 1 mL, 26 mmol), followed by sodium methoxide (20 mL of 25% in methanol). After the collection of the precipitate, the filtrate was concentrated under reduced pressure, and the residue was mixed with methanol (50 mL). The resulting solid was isolated by filtration, and the isolated solids were combined to provide 2.3 g of methyl 3-(4-amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanoate.

Part C

A solution of potassium hydroxide (20 mL of a 0.5 M solution in methanol) was added to a mixture of methyl 3-(4-amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanoate (1.7 g, 5.4 mmol) and methanol (50 mL), and the resulting solution was heated at reflux for one day, allowed to cool, stirred for three days and ambient temperature, heated at reflux for one day, and allowed to cool. Hydrogen chloride (11 mL of a 1 N solution in diethyl ether) was added, and the reaction was stirred for 15 minutes. The solvents were removed under reduced pressure, and the residue was dissolved in dichloromethane (50 mL) and three drops of DMF. A solution of oxalyl chloride (0.96 mL, 11 mmol) in dichloromethane (10 mL) was added rapidly, and the solution was stirred for three days at ambient temperature and then concentrated under reduced pressure. The residue was dissolved in dichloromethane (50 mL), and ammonia (15 mL of a 0.5 M solution in 1,4-dioxane) was added. The reaction was stirred for 30 minutes, and then additional ammonia (10 mL of a 7 N solution in methanol) was added. The reaction was stirred overnight at ambient temperature and concentrated under reduced pressure. The solid residue was stirred with saturated aqueous sodium bicarbonate (50 mL) for 15 minutes, isolated by filtration, washed with saturated aqueous sodium bicarbonate (50 mL), and recrystallized from methanol/water containing a few mL of 0.5 M potassium hydroxide in methanol. The resulting crystals were mixed with material from a separate run, and the combined solids were dried overnight in a vacuum oven at 80 °C, washed with water (3 x 15 mL), and recrystallized from a mixture of methanol (20 mL), water (7 mL), and 0.5 N potassium hydroxide in methanol (3 mL). The crystals were dried overnight in

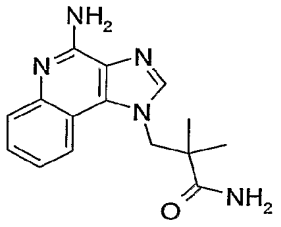
a vacuum oven at 80 °C to provide 3-(4-amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanamide as light yellow crystals, mp 284-287 °C.

MS (APCI) *m/z* 298 ($M + H^+$);

Anal. calcd for $C_{16}H19N_5O$: C, 64.63; H, 6.44; N, 23.55. Found: C, 64.37; H, 6.37; N, 23.54.

Example 62

3-(4-Amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanamide



Part A

Ethyl 3-(3-aminoquinolin-4-ylamino)-2,2-dimethylpropanoate (see Example 26 Parts A through D, 5.3 g, 18 mmol) was treated according to a modification of the method described in Part B of Example 8 using trimethyl orthoformate in lieu of trimethyl orthobutyrate. Prior to the addition of trimethyl orthoformate (3.0 mL, 27 mmol) and pyridinium *p*-toluenesulfonate (0.050 g), the reaction was heated at reflux for 15 minutes. The reaction was heated at reflux overnight, allowed to cool to ambient temperature, washed with saturated aqueous sodium bicarbonate (2 x 35 mL), and extracted with water (45 mL) containing 10% hydrochloric acid (5 mL). The acidic extract was made basic with the addition of potassium carbonate and then extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide 4.3 g of ethyl 3-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanoate as an oil.

Part B

A modification of the methods described in Part B of Example 60 was used to treat ethyl 3-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanoate (4.3 g, 14 mmol) with mCPBA (6.3 g of 77% pure material), followed by trichloroacetyl isocyanate (2.0 mL, 17 mmol). The reaction with the isocyanate was stirred for two hours before the addition of additional trichloroacetyl isocyanate (1.0 mL) and stirring for an additional two hours.

After the reaction with sodium methoxide (11 mL of 25% in methanol), the solvent was removed under reduced pressure. The residue was mixed with methanol (25 mL), and the mixture was cooled to 0 °C and filtered to isolate 1.61 g of methyl 3-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanoate as a solid. The filtrate was concentrated under reduced pressure, and the residue was mixed with saturated aqueous sodium bicarbonate (100 mL). A precipitate formed, was isolated by filtration, and was mixed with concentrated hydrochloric acid to adjust to pH 7. The precipitate was again isolated by filtration and dissolved in dichloromethane. The resulting solution was dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide an additional 1.51 g of methyl 3-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanoate as an oil.

Part C

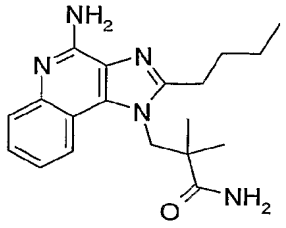
A modification of the methods described in Part C of Example 61 was used to treat methyl 3-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanoate (1.61 g, 5.4 mmol) with potassium hydroxide (22 mL of 0.5 M); the reaction was heated at reflux overnight. The reaction with oxalyl chloride (0.96 mL) in dichloromethane (55 mL total) was stirred for one hour before more oxalyl chloride (1.0 mL) and DMF (three drops) were added, and then the reaction was stirred overnight. The precipitate isolated after the reaction with ammonia and treatment with sodium bicarbonate was combined with material from another run and recrystallized from methanol/water. The resulting solid was isolated by filtration and heated gently in a mixture of methanol (35 mL), water (10 mL), and concentrated hydrochloric acid (0.83 mL). The mixture was filtered to remove a small amount of insoluble material, and a precipitate formed in the filtrate. The precipitate was isolated by filtration, recrystallized twice from methanol/water, dried overnight in a vacuum oven at 70 °C, and recrystallized four times from ethyl acetate/methanol/water with a filtration through a 20 micron filter prior to the last two crystallizations. The resulting crystals were dried overnight in a vacuum oven at 70 °C to provide 3-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanamide as white crystals, mp 287-289 °C.

MS (APCI) *m/z* 284 ($M + H^+$);

Anal. calcd for $C_{15}H_{17}N_5O \cdot 1.0\ HCl \cdot 1.0\ H_2O$: C, 53.33; H, 5.97; N, 20.73. Found: C, 53.25; H, 5.85; N, 20.60.

Example 63

3-(4-Amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanamide



Part A

Ethyl 3-(3-aminoquinolin-4-ylamino)-2,2-dimethylpropanoate (see Example 26 Parts A through D, 9.0 g, 31.3 mmol) was treated according to a modification of the method described in Part B of Example 8 using trimethyl orthovalerate in lieu of trimethyl orthobutyrate. Prior to the addition of trimethyl orthovalerate (6.1 mL, 35 mmol) and pyridinium *p*-toluenesulfonate (0.050 g), the reaction was heated at reflux for 15 minutes and then cooled slightly. The reaction was heated at reflux for five hours, allowed to cool to ambient temperature, stirred overnight, and concentrated under reduced pressure to provide 11.2 g of ethyl 3-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanoate.

Part B

A modification of the methods described in Part B of Example 60 was used to treat ethyl 3-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanoate (11.0 g, 31 mmol) with mCPBA (13.6 g of 77% pure material), followed by trichloroacetyl isocyanate (4.4 mL, 37 mmol). The reaction with the isocyanate was stirred for 1.5 hours before the addition of additional trichloroacetyl isocyanate (4.4 mL) and stirring for three days. Additional trichloroacetyl isocyanate (0.5 mL) was added, and the reaction was stirred for four hours. After the addition of methanol (50 mL), the solution was stirred overnight, and then the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (150 mL), and the solution was washed with saturated aqueous sodium bicarbonate (2 x 35 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with 5% methanol in dichloromethane containing 2 mL ammonium hydroxide per liter of eluent) to provide 11.4 g of methyl 3-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanoate as a semi-solid.

Part C

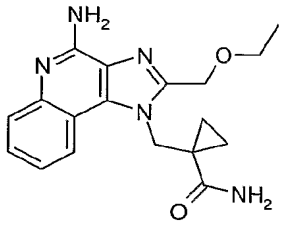
A modification of the methods described in Part C of Example 60 was used to treat methyl 3-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanoate (7.6 g, 21 mmol) with potassium hydroxide (44 mL of 0.5 M); additional potassium hydroxide (22 mL) was added after refluxing for four hours. After the reaction was heated at reflux for five days, additional potassium hydroxide (11 mL) was added, and the reaction was heated for four more hours. After the reaction with oxalyl chloride (3.7 mL, 42 mmol) was stirred overnight, additional oxalyl chloride (1.0 mL) was added, and then the reaction was stirred for two hours. After the addition of ammonia in methanol (35 mL), the reaction was stirred for one hour and then concentrated. The residue was stirred with saturated aqueous sodium bicarbonate for 30 minutes, isolated by filtration, and recrystallized three times from methanol/water. During the first recrystallization, a solution in methanol was filtered through a 20 micron filter prior to the addition of water. The resulting crystals were dried overnight in a vacuum oven at 70 °C to provide 1.60 g of 3-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanamide as light tan crystals, mp 231-233 °C.

MS (APCI) *m/z* 340 ($M + H^+$);

Anal. calcd for $C_{19}H_{25}N_5O$: C, 67.23; H, 7.42; N, 20.63. Found: C, 66.85; H, 7.56; N, 20.67.

Example 64

1-{[4-Amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]methyl}cyclopropanecarboxamide



Part A

Ethylcyanoacetate (15.0 mL, 141 mmol) was added to a mixture of potassium carbonate (48.7 g, 353 mmol) and acetone (200 mL), and 1,2-dibromoethane (13.4 mL, 155 mmol) was added dropwise to the resulting mixture over a period of eight minutes.

The reaction was heated at reflux overnight. An analysis by TLC indicated the presence of ethylcyanoacetate, and additional 1,2-dibromoethane (1.8 mL, 0.15 equivalent) was added. The reaction mixture was heated at reflux for an additional four hours and filtered through a layer of CELITE filter agent. The filter cake was washed with acetone (200 mL), and the combined filtrates were concentrated under reduced pressure to provide ethyl 1-cyanocyclopropanecarboxylate as an orange oil containing about 10 mole % 1,2-dibromoethane.

Part B

Platinum (IV) oxide (0.98 g) and concentrated hydrochloric acid (25 mL) were added to a solution of the material from Part A in ethanol (225 mL), and the mixture was placed under hydrogen pressure (40 psi, 2.8 x 10^5 Pa) on a Parr apparatus and shaken for 20 hours and then filtered through a layer of CELITE filter agent. The filter cake was washed with methanol (200 mL), and the combined filtrates were concentrated under reduced pressure. The residue was three times dissolved in methanol and concentrated and then twice dissolved in toluene and concentrated to afford ethyl 1-(aminomethyl)cyclopropanecarboxylate hydrochloride as a thick, pale yellow oil.

Part C

A suspension of 4-chloro-3-nitroquinoline (24.5 g, 118 mmol) and triethylamine (41 mL, 294 mmol) in dichloromethane (450 mL) was cooled to 5 °C, and a solution of the material from Part B in dichloromethane (200 mL) was added over a period of 15 minutes. The reaction was stirred at 5 °C for one hour, allowed to warm to ambient temperature, stirred overnight, and washed with saturated aqueous sodium bicarbonate (250 mL). The aqueous layer was extracted with dichloromethane (2 x 50 mL), and the combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting orange oil was recrystallized from acetonitrile to provide 21.47 g of ethyl 1-{[(3-nitroquinolin-4-yl)amino]methyl}cyclopropanecarboxylate as a bright yellow solid.

Part D

A suspension of 5% platinum on carbon (0.80 g) and ethyl 1-{[(3-nitroquinolin-4-yl)amino]methyl}cyclopropanecarboxylate (8.0 g, 25 mmol) in ethyl acetate was placed under hydrogen pressure (30 psi, 2.1 x 10^5 Pa) on a Parr apparatus for three hours and filtered through a layer of CELITE filter agent. The filter cake was washed with ethyl

acetate (50 mL), and the combined filtrates were concentrated under reduced pressure to provide ethyl 1-{[(3-aminoquinolin-4-yl)amino]methyl}cyclopropanecarboxylate as a yellow solid.

Part E

A solution of the material from Part D in dichloromethane (100 mL) was cooled to 0 °C, and ethoxyacetyl chloride (2.9 mL, 28 mmol) was added dropwise over a period of five minutes. The reaction was allowed to slowly warm to ambient temperature, stirred overnight, and concentrated under reduced pressure to provide ethyl 1-[({3-[(ethoxyacetyl)amino]quinolin-4-yl}amino)methyl]cyclopropanecarboxylate hydrochloride.

Part F

Triethylamine (10.6 mL, 76.2 mmol) was added to a solution from Part E in ethanol (100 mL), and the reaction was heated at 60 °C overnight. The solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane (100 mL). The resulting solution was washed with saturated aqueous sodium bicarbonate (75 mL). The aqueous fraction was extracted with dichloromethane (2 x 35 mL), and the combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide ethyl 1-{[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]methyl}cyclopropanecarboxylate as a brown semi-solid.

Part G

Aqueous sodium hydroxide (8.5 mL of 6 M) was added to a solution of the material from Part F in ethanol (80 mL); the reaction was stirred at ambient temperature for three hours and concentrated under reduced pressure. The residue was mixed with water (60 mL) and adjusted to pH 5 with the addition of 2 M hydrochloric acid. No precipitate formed, and the mixture was adjusted to pH 12 and washed with diethyl ether (3 x 20 mL). The solution was adjusted to pH 4, and a precipitate formed and was isolated by filtration and dried to provide 4.36 g of 1-{[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]methyl}cyclopropanecarboxylic acid. The filtrate was adjusted to pH 7 and extracted with chloroform (3 x 20 mL), and the combined extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide an orange solid. The solid was triturated with acetonitrile and isolated by filtration to provide an

additional 1.76 g of 1-{[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]methyl}cyclopropanecarboxylic acid.

Part H

Oxalyl chloride (1.6 mL, 18 mmol) was added dropwise over a period of 5 minutes to a suspension of 1-{[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]methyl}cyclopropanecarboxylic acid (2.0 g, 6.2 mmol) in dichloromethane (50 mL) containing one drop of DMF. The reaction mixture was stirred for two hours and then concentrated under reduced pressure to provide 1-{[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]methyl}cyclopropanecarbonyl chloride.

Part I

A solution of the material from Part H in dichloromethane (35 mL) was cooled to 0 °C, and a solution of ammonia in 1,4-dioxane (18.5 mL of 0.5 M) was added. The reaction was stirred for ten minutes, and then ammonia gas was bubbled through the solution for ten minutes. The reaction was then sealed, allowed to warm to ambient temperature slowly, and stirred overnight. The solvent was removed under reduced pressure, and the residue was triturated with 1 M aqueous sodium hydroxide and isolated by filtration to provide 1.70 g of 1-{[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]methyl}cyclopropanecarboxamide as an off-white solid.

Part J

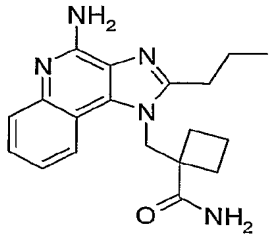
mCPBA (1.68 g, 6.81 mmol) was added to a suspension of 1-{[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]methyl}cyclopropanecarboxamide (1.70 g, 5.24 mmol) in chloroform (25 mL); the reaction was stirred for two hours at ambient temperature and then cooled to 0 °C. Ammonium hydroxide (5 mL) and *p*-toluenesulfonyl chloride (1.10 g, 5.76 mmol) were added. The reaction was stirred for one hour at 5 °C and then filtered to isolate a precipitate. The precipitate was triturated with 2 M aqueous sodium hydroxide, isolated by filtration, triturated with hot acetonitrile, isolated by filtration, and recrystallized from ethanol. The crystals were dried overnight at 85 °C in a vacuum oven to provide 0.78 g of 1-{[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]methyl}cyclopropanecarboxamide as tan needles, mp 230.5-232.5 °C.

MS (ESI) *m/z* 340 $(M + H)^+$;

Anal. calcd for $C_{18}H_{21}N_5O_2$: C, 63.70; H, 6.24; N, 20.63. Found: C, 63.65; H, 6.31; N, 20.57.

Example 65

1-[(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]cyclobutanecarboxamide



Part A

The method described in Part A of Example 64 was used to treat ethylcyanoacetate (45 mL, 420 mmol) with 1,3-dibromopropane (51 mL, 510 mmol) and potassium carbonate (146 g, 1.06 mol) to provide ethyl 1-cyanocyclobutanecarboxylate as an orange oil containing about 15 mole % 1,2-dibromopropane.

Part B

The method described in Part B of Example 64 was used to hydrogenate (30 psi, 2.1 x 10^5 Pa) the material from Part A for 28 hours in the presence of platinum (IV) oxide (2.0 g) and concentrated hydrochloric acid (70 mL) to provide ethyl 1-(aminomethyl)cyclobutanecarboxylate hydrochloride as a thick, pale yellow oil.

Part C

A modification of the method described in Part C of Example 64 was used to treat the material from Part B with 4-chloro-3-nitroquinoline (73.6 g, 353 mmol) and triethylamine (147 mL, 1.06 mol). The crude product was divided into three portions, and each portion was purified by chromatography on 175 g of silica gel (eluting with 25-40% ethyl acetate in hexane). The resulting yellow-orange solid was triturated with acetonitrile and isolated by filtration to provide 27.56 g of ethyl 1-{[(3-nitroquinolin-4-yl)amino]methyl}cyclobutanecarboxylate as a bright yellow solid.

Part D

The method described in Part D of Example 64 was used to hydrogenate (35 psi, 2.4 x 10^5 Pa) ethyl 1-{[(3-nitroquinolin-4-yl)amino]methyl}cyclobutanecarboxylate (10.0 g, 30.4 mmol) in the presence of 5% platinum on carbon (1.0 g) to provide ethyl 1-{[(3-aminoquinolin-4-yl)amino]methyl}cyclobutanecarboxylate as a yellow solid.

Part E

Trimethyl orthobutyrate (5.0 mL, 32 mmol) and pyridine hydrochloride (0.14 g, 1.2 mmol) were added to a suspension of the material from Part D in toluene (100 mL), and the reaction was heated at reflux for two hours, allowed to cool to ambient temperature, and concentrated under reduced pressure. The crude product was triturated with acetonitrile and isolated by filtration to provide 7.55 g of ethyl 1-[(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]cyclobutanecarboxylate as a white solid.

Part F

Aqueous sodium hydroxide (7 mL of 6 M) was added to a solution of ethyl 1-[(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]cyclobutanecarboxylate (7.55 g, 21.5 mmol) in ethanol (60 mL); the reaction was stirred at ambient temperature for one hour and concentrated under reduced pressure. The residue was dissolved in water (40 mL) and adjusted to pH 7 with the addition of 2 M hydrochloric acid. A precipitate formed, was isolated by filtration, and dried in a vacuum oven at 70 °C for two hours to provide 6.76 g of 1-[(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]cyclobutanecarboxylic acid as a tan solid.

Part G

The methods described in Parts H and I of Example 64 were used to treat 1-[2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]cyclobutanecarboxylic acid (1.75 g, 5.41 mmol) with oxalyl chloride (1.4 mL, 16 mmol) followed by ammonia and to isolate the final product, 1-[(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]cyclobutanecarboxamide as an off-white solid (1.81 g).

Part H

The method described in Part J of Example 64 was used to treat the material from Part G with mCPBA (1.73 g, 7.03 mmol) followed by ammonium hydroxide (6 mL) and *p*-toluenesulfonyl chloride (1.13 g, 5.95 mmol). At the completion of the reaction, the mixture was filtered to remove a solid impurity. The filtrate was diluted with chloroform (20 mL) and washed with saturated aqueous sodium bicarbonate (40 mL). The aqueous fraction was extracted with chloroform (2 x 15 mL), and the combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was triturated with acetonitrile and isolated by filtration. The resulting solid was dissolved in 10% methanol in chloroform and treated with activated charcoal. After

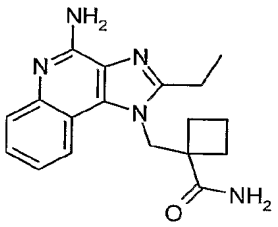
filtration, the solution was purified by chromatography on a HORIZON HPFC system (40+M cartridge, eluting with 0 to 55% CMA in chloroform), and the resulting white solid was triturated with acetonitrile, isolated by filtration, and dried in a vacuum oven at 85 °C to provide 0.859 g of 1-[(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]cyclobutanecarboxamide as a white powder, mp 234-237 °C.

MS (ESI) *m/z* 338 $(M + H)^+$;

Anal. calcd for $C_{19}H_{23}N_5O$: C, 67.63; H, 6.87; N, 20.76. Found: C, 67.43; H, 7.12; N, 21.00.

Example 66

1-[(4-Amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]cyclobutanecarboxamide



Part A

The method desribed in Part E of Example 65 was used to treat ethyl 1-{[(3-aminoquinolin-4-yl)amino]methyl}cyclobutanecarboxylate (6 mmol) with triethyl orthopropionate (1.6 mL, 7.9 mmol) and pyridine hydrochloride (35 mg) and isolate the final product, ethyl 1-[(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]cyclobutanecarboxylate (1.86 g, 5.51 mmol), as a white solid, which was treated with sodium hydroxide (1.8 mL of 6 M) according to the method of Part F of Example 65. The product, 1-[(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]cyclobutanecarboxylic acid, was isolated as a tan solid (1.49 g) according to the methods of Part F of Example 65.

Part B

A modification of the method described in Parts H of Example 64 was used to treat 1-[2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]cyclobutanecarboxylic acid (1.49 g, 4.61 mmol) with oxalyl chloride (1.2 mL, 14 mmol) in dichloromethane (30 mL). After the reaction was stirred for 1.5 hours, additional oxalyl chloride (0.6 mL) was added. The product was carried on as a mixture of the carboxylic acid and the acid chloride, which was treated according to the method of Part I of Example 64 to provide 0.66 g of 1-[(2-

ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]cyclobutanecarboxamide as an off-white solid.

Part C

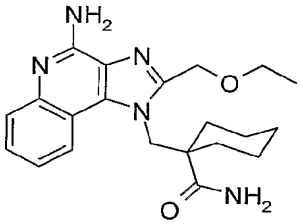
The method described in Part J of Example 64 was used to treat the material from Part B with mCPBA (0.69 g, 2.8 mmol) followed by ammonium hydroxide (3 mL) and *p*-toluenesulfonyl chloride (0.45 g, 2.35 mmol). At the completion of the reaction, the precipitated product was isolated by filtration, triturated with 1 M aqueous sodium hydroxide, and isolated by filtration. The resulting tan solid was purified by chromatography on a HORIZON HPFC system (40+M cartridge, eluting with 0 to 65% CMA in chloroform), and the resulting white solid was triturated with hot acetonitrile, isolated by filtration, and dried in a vacuum oven at 85 °C to provide 0.218 g of 1-[(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]cyclobutanecarboxamide as a white powder, mp 227-230 °C.

MS (ESI) *m/z* 324 $(M + H)^+$;

Anal. calcd for $C_{18}H_{21}N_5O$: C, 66.85; H, 6.55; N, 21.66. Found: C, 66.92; H, 6.72; N, 21.83.

Example 67

1-{[4-Amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]methyl}cyclohexanecarboxamide



Part A

Potassium carbonate (30.4 g, 0.220 mol) and 1,5-dibromopentane (13.6 mL, 0.100 mol) were sequentially added to a solution of ethylcyanoacetate (10.6 mL, 0.100 mol) in DMF (100 mL), and the reaction was stirred overnight at ambient temperature. The reaction mixture was partitioned between water and ethyl acetate, and the organic fraction was separated, washed with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide ethyl 1-cyanocyclohexanecarboxylate.

Part B

Platinum (IV) oxide (1.72 g) was added to a solution of ethyl 1-cyanocyclohexanecarboxylate (17.15 g, 94.6 mmol) in concentrated hydrochloric acid (20 mL) and ethanol (200 mL), and the mixture was placed under hydrogen pressure on a Parr apparatus and shaken for 20 hours. The solvent was removed under reduced pressure, and the residue was diluted with water. The resulting mixture was adjusted to pH 7 with the addition of solid sodium carbonate and then extracted several times with dichloromethane. The combined extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 5.67 g of ethyl 1-(aminomethyl)cyclohexanecarboxylate as a colorless oil. A portion of the water was removed from the aqueous layer, and dichloromethane was added. The mixture was stirred overnight at ambient temperature, and the organic fraction was separated, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 11.69 g of ethyl 1-(aminomethyl)cyclohexanecarboxylate hydrochloride as a white solid.

Part C

A solution of 4-chloro-3-nitroquinoline (10.96 g, 52.5 mmol) in dichloromethane (200 mL) was cooled to approximately 0 °C, and triethylamine (22.0 mL, 158 mmol) and a solution of ethyl 1-(aminomethyl)cyclohexanecarboxylate hydrochloride (11.65 g, 52.5 mmol) in dichloromethane (30 mL) were sequentially added. The reaction was stirred for four hours, and the solvent was removed under reduced pressure. The residue was stirred in deionized water (50 mL) for one hour, and the mixture was extracted several times with dichloromethane. The combined extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting orange oil was purified by chromatography on silica gel (eluting with 3-5% methanol in dichloromethane) to provide 11.72 g of ethyl 1-{[(3-nitroquinolin-4-yl)amino]methyl}cyclohexanecarboxylate as an orange oil that solidified upon standing.

Part D

A suspension of 5% platinum on carbon (1.2 g) and ethyl 1-{[(3-nitroquinolin-4-yl)amino]methyl}cyclohexanecarboxylate (11.7 g, 32.7 mmol) in acetonitrile (100 mL) was placed under hydrogen pressure (3 atm, 2.1 x 10^5 Pa) on a Parr apparatus for five hours and filtered through a layer of CELITE filter agent. The filtrate was concentrated

under reduced pressure to provide 9.60 g of ethyl 1-{[(3-aminoquinolin-4-yl)amino]methyl}cyclohexanecarboxylate as an orange oil that solidified upon standing.

Part E

A solution of ethoxyacetyl chloride (3.95 g, 32.3 mmol) in acetonitrile (10 mL) was added to a solution of ethyl 1-{[(3-aminoquinolin-4-yl)amino]methyl}cyclohexanecarboxylate (9.60 g, 29.3 mmol) in acetonitrile (200 mL), and the resulting mixture was stirred for five hours at ambient temperature. A precipitate was present and was isolated by filtration, washed with cold acetonitrile, and dried overnight under vacuum to provide 10.18 g of ethyl 1-[({3-[(ethoxyacetyl)amino]quinolin-4-yl}amino)methyl]cyclohexanecarboxylate hydrochloride.

Part F

Sodium hydroxide (2.71 g, 67.7 mmol) was added to a solution of ethyl 1-[({3-[(ethoxyacetyl)amino]quinolin-4-yl}amino)methyl]cyclohexanecarboxylate hydrochloride (10.15 g, 22.6 mmol) in 9:1 ethanol/water (30 mL), and the solution was heated at reflux for several hours. The ethanol was removed under reduced pressure, and the resulting solution was diluted with water and adjusted to pH 4 to 5 with the addition of 3 M hydrochloric acid. The mixture was then extracted several times with dichloromethane. The aqueous fraction was adjusted to pH 7 and extracted several more times with dichloromethane. The combined extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 5.73 g of 1-{[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]methyl}cyclohexanecarboxylic acid.

Part G

Excess oxalyl chloride was added to a suspension of 1-{[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]methyl}cyclohexanecarboxylic acid (1.30 g, 3.54 mmol) in chloroform, and the reaction mixture was heated at 60 °C overnight under an argon atmosphere. The volatiles were removed under reduced pressure, and chloroform was added to the residue. An excess of ammonia (0.5 M in 1,4-dioxane) was added, and the reaction mixture was stirred for two hours. The volatiles were removed under reduced pressure, and the residue was purified by column chromatography on silica gel to provide 1.30 g of 1-{[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]methyl}cyclohexanecarboxamide.

Part H

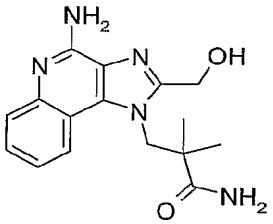
mCPBA (953 mg of 77% pure material, 4.25 mmol) was added to a solution of 1-{[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]methyl}cyclohexanecarboxamide (1.30 g, 3.54 mmol) in chloroform (15 mL); the reaction was stirred for one hour at ambient temperature. Ammonium hydroxide (15 mL) and *p*-toluenesulfonyl chloride (742 mg, 3.89 mmol) were added, and the mixture was stirred vigorously for two hours. The aqueous fraction was separated and extracted several times with chloroform. The combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with 2-7% methanol in dichloromethane) followed by recrystallization from acetonitrile to provide 1-{[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]methyl}cyclohexanecarboxamide as a tan crystalline solid, mp 221-223 °C.

MS (APCI) *m/z* 382 ($M + H^+$);

Anal. calcd for $C_{20}H_{25}N_5O_3$ (with 0.25 eq. NH_4): C, 65.35; H, 7.31; N, 19.05. Found: C, 64.87; H, 6.85; N, 18.95.

Example 68

3-[4-Amino-2-(hydroxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanamide



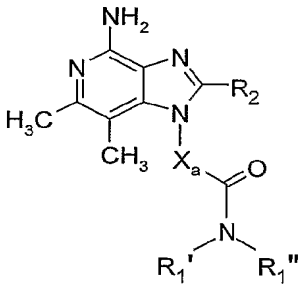
Boron tribromide (15 mL of a 1 N solution in dichloromethane) was added to a solution of 3-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanamide (1.1 g, 3.2 mmol, Example 28) in 1,2-dichloroethane (35 mL). The reaction was heated at reflux for 35 minutes, cooled to approximately 0 °C, and adjusted to pH 8 with the addition of a solution of potassium hydroxide (90 mL of a 0.5 N solution in methanol). The volatiles were removed under reduced pressure, and the residue was mixed with methanol (50 mL) and isolated by filtration. The filtrate was concentrated under reduced pressure, and the residue was stirred overnight with saturated aqueous

sodium bicarbonate (35 mL). The resulting solid was isolated by filtration, combined with material from another run, and purified by column chromatography on silica gel (eluting with 20% methanol in dichloromethane containing 1% ammonium hydroxide) and dried in a vacuum oven for three hours at 60 °C to provide 3-[4-amino-2-(hydroxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropanamide as white crystals, mp 201-203 °C. MS (APCI) *m/z* 314 ($M + H^+$);

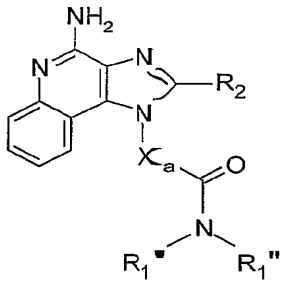
Anal. calcd for $C_{16}H_{19}N_5O \cdot 0.47\ H_2O \cdot 0.24\ CH_3OH$: C, 59.22; H, 6.33; N, 21.26. Found: C, 59.37; H, 6.35; N, 21.26.

Exemplary Compounds

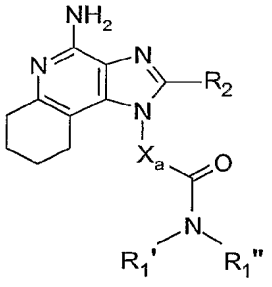
Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas (IIIa, IVd, Vc, or VIb) and the following R_1', R_1'', X_a, and R_2 substituents, wherein each line of the table is matched with Formula IIIa, IVd, Vc, or VIb to represent a specific embodiment of the invention.



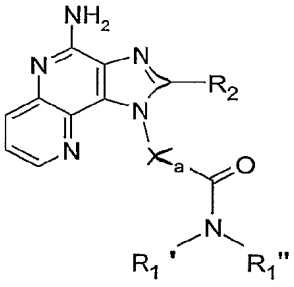
IIIa



IVd



Vc



VIb

R_1'	R_1''	X_a	R_2
hydrogen	hydrogen	$-(CH_2)-$	methyl
hydrogen	hydrogen	$-(CH_2)-$	ethyl
hydrogen	hydrogen	$-(CH_2)-$	n-propyl

hydrogen	hydrogen	-(CH_2)-	n-butyl
hydrogen	hydrogen	-(CH_2)-	ethoxymethyl
hydrogen	hydrogen	-(CH_2)-	2-methoxyethyl
hydrogen	hydrogen	-$(CH_2)_2$-	methyl
hydrogen	hydrogen	-$(CH_2)_2$-	ethyl
hydrogen	hydrogen	-$(CH_2)_2$-	n-propyl
hydrogen	hydrogen	-$(CH_2)_2$-	n-butyl
hydrogen	hydrogen	-$(CH_2)_2$-	ethoxymethyl
hydrogen	hydrogen	-$(CH_2)_2$-	2-methoxyethyl
hydrogen	hydrogen	-$(CH_2)_3$-	methyl
hydrogen	hydrogen	-$(CH_2)_3$-	ethyl
hydrogen	hydrogen	-$(CH_2)_3$-	n-propyl
hydrogen	hydrogen	-$(CH_2)_3$-	n-butyl
hydrogen	hydrogen	-$(CH_2)_3$-	ethoxymethyl
hydrogen	hydrogen	-$(CH_2)_3$-	2-methoxyethyl
hydrogen	hydrogen	-$CH_2C(CH_3)_2$-	methyl
hydrogen	hydrogen	-$CH_2C(CH_3)_2$-	ethyl
hydrogen	hydrogen	-$CH_2C(CH_3)_2$-	n-propyl
hydrogen	hydrogen	-$CH_2C(CH_3)_2$-	n-butyl
hydrogen	hydrogen	-$CH_2C(CH_3)_2$-	ethoxymethyl
hydrogen	hydrogen	-$CH_2C(CH_3)_2$-	2-methoxyethyl
hydrogen	hydrogen	-$CH_2C(CH_3)_2CH_2$-	methyl
hydrogen	hydrogen	-$CH_2C(CH_3)_2CH_2$-	ethyl
hydrogen	hydrogen	-$CH_2C(CH_3)_2CH_2$-	n-propyl
hydrogen	hydrogen	-$CH_2C(CH_3)_2CH_2$-	n-butyl
hydrogen	hydrogen	-$CH_2C(CH_3)_2CH_2$-	ethoxymethyl
hydrogen	hydrogen	-$CH_2C(CH_3)_2CH_2$-	2-methoxyethyl
hydrogen	methyl	-(CH_2)-	methyl
hydrogen	methyl	-(CH_2)-	ethyl
hydrogen	methyl	-(CH_2)-	n-propyl
hydrogen	methyl	-(CH_2)-	n-butyl
hydrogen	methyl	-(CH_2)-	ethoxymethyl
hydrogen	methyl	-(CH_2)-	2-methoxyethyl
hydrogen	methyl	-$(CH_2)_2$-	methyl
hydrogen	methyl	-$(CH_2)_2$-	ethyl
hydrogen	methyl	-$(CH_2)_2$-	n-propyl
hydrogen	methyl	-$(CH_2)_2$-	n-butyl
hydrogen	methyl	-$(CH_2)_2$-	ethoxymethyl
hydrogen	methyl	-$(CH_2)_2$-	2-methoxyethyl
hydrogen	methyl	-$(CH_2)_3$-	methyl
hydrogen	methyl	-$(CH_2)_3$-	ethyl
hydrogen	methyl	-$(CH_2)_3$-	n-propyl
hydrogen	methyl	-$(CH_2)_3$-	n-butyl
hydrogen	methyl	-$(CH_2)_3$-	ethoxymethyl
hydrogen	methyl	-$(CH_2)_3$-	2-methoxyethyl
hydrogen	methyl	-$CH_2C(CH_3)_2$-	methyl
hydrogen	methyl	-$CH_2C(CH_3)_2$-	ethyl
hydrogen	methyl	-$CH_2C(CH_3)_2$-	n-propyl
hydrogen	methyl	-$CH_2C(CH_3)_2$-	n-butyl
hydrogen	methyl	-$CH_2C(CH_3)_2$-	ethoxymethyl

hydrogen	methyl	$-CH_2C(CH_3)_2-$	2-methoxyethyl
hydrogen	methyl	$-CH_2C(CH_3)_2CH_2-$	methyl
hydrogen	methyl	$-CH_2C(CH_3)_2CH_2-$	ethyl
hydrogen	methyl	$-CH_2C(CH_3)_2CH_2-$	n-propyl
hydrogen	methyl	$-CH_2C(CH_3)_2CH_2-$	n-butyl
hydrogen	methyl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
hydrogen	methyl	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
methyl	methyl	$-(CH_2)-$	methyl
methyl	methyl	$-(CH_2)-$	ethyl
methyl	methyl	$-(CH_2)-$	n-propyl
methyl	methyl	$-(CH_2)-$	n-butyl
methyl	methyl	$-(CH_2)-$	ethoxymethyl
methyl	methyl	$-(CH_2)-$	2-methoxyethyl
methyl	methyl	$-(CH_2)_2-$	methyl
methyl	methyl	$-(CH_2)_2-$	ethyl
methyl	methyl	$-(CH_2)_2-$	n-propyl
methyl	methyl	$-(CH_2)_2-$	n-butyl
methyl	methyl	$-(CH_2)_2-$	ethoxymethyl
methyl	methyl	$-(CH_2)_2-$	2-methoxyethyl
methyl	methyl	$-(CH_2)_3-$	methyl
methyl	methyl	$-(CH_2)_3-$	ethyl
methyl	methyl	$-(CH_2)_3-$	n-propyl
methyl	methyl	$-(CH_2)_3-$	n-butyl
methyl	methyl	$-(CH_2)_3-$	ethoxymethyl
methyl	methyl	$-(CH_2)_3-$	2-methoxyethyl
methyl	methyl	$-CH_2C(CH_3)_2-$	methyl
methyl	methyl	$-CH_2C(CH_3)_2-$	ethyl
methyl	methyl	$-CH_2C(CH_3)_2-$	n-propyl
methyl	methyl	$-CH_2C(CH_3)_2-$	n-butyl
methyl	methyl	$-CH_2C(CH_3)_2-$	ethoxymethyl
methyl	methyl	$-CH_2C(CH_3)_2-$	2-methoxyethyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	methyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	n-propyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	n-butyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
ethyl	hydrogen	$-(CH_2)-$	methyl
ethyl	hydrogen	$-(CH_2)-$	ethyl
ethyl	hydrogen	$-(CH_2)-$	n-propyl
ethyl	hydrogen	$-(CH_2)-$	n-butyl
ethyl	hydrogen	$-(CH_2)-$	ethoxymethyl
ethyl	hydrogen	$-(CH_2)-$	2-methoxyethyl
ethyl	hydrogen	$-(CH_2)_2-$	methyl
ethyl	hydrogen	$-(CH_2)_2-$	ethyl
ethyl	hydrogen	$-(CH_2)_2-$	n-propyl
ethyl	hydrogen	$-(CH_2)_2-$	n-butyl
ethyl	hydrogen	$-(CH_2)_2-$	ethoxymethyl
ethyl	hydrogen	$-(CH_2)_2-$	2-methoxyethyl
ethyl	hydrogen	$-(CH_2)_3-$	methyl

ethyl	hydrogen	$-(CH_2)_3-$	ethyl
ethyl	hydrogen	$-(CH_2)_3-$	n-propyl
ethyl	hydrogen	$-(CH_2)_3-$	n-butyl
ethyl	hydrogen	$-(CH_2)_3-$	ethoxymethyl
ethyl	hydrogen	$-(CH_2)_3-$	2-methoxyethyl
ethyl	hydrogen	$-CH_2C(CH_3)_2-$	methyl
ethyl	hydrogen	$-CH_2C(CH_3)_2-$	ethyl
ethyl	hydrogen	$-CH_2C(CH_3)_2-$	n-propyl
ethyl	hydrogen	$-CH_2C(CH_3)_2-$	n-butyl
ethyl	hydrogen	$-CH_2C(CH_3)_2-$	ethoxymethyl
ethyl	hydrogen	$-CH_2C(CH_3)_2-$	2-methoxyethyl
ethyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	methyl
ethyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethyl
ethyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	n-propyl
ethyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	n-butyl
ethyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
ethyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
ethyl	methyl	$-(CH_2)-$	methyl
ethyl	methyl	$-(CH_2)-$	ethyl
ethyl	methyl	$-(CH_2)-$	n-propyl
ethyl	methyl	$-(CH_2)-$	n-butyl
ethyl	methyl	$-(CH_2)-$	ethoxymethyl
ethyl	methyl	$-(CH_2)-$	2-methoxyethyl
ethyl	methyl	$-(CH_2)_2-$	methyl
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ethyl	methyl	$-(CH_2)_2-$	n-butyl
ethyl	methyl	$-(CH_2)_2-$	ethoxymethyl
ethyl	methyl	$-(CH_2)_2-$	2-methoxyethyl
ethyl	methyl	$-(CH_2)_3-$	methyl
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ethyl	methyl	$-(CH_2)_3-$	n-propyl
ethyl	methyl	$-(CH_2)_3-$	n-butyl
ethyl	methyl	$-(CH_2)_3-$	ethoxymethyl
ethyl	methyl	$-(CH_2)_3-$	2-methoxyethyl
ethyl	methyl	$-CH_2C(CH_3)_2-$	methyl
ethyl	methyl	$-CH_2C(CH_3)_2-$	ethyl
ethyl	methyl	$-CH_2C(CH_3)_2-$	n-propyl
ethyl	methyl	$-CH_2C(CH_3)_2-$	n-butyl
ethyl	methyl	$-CH_2C(CH_3)_2-$	ethoxymethyl
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ethyl	methyl	$-CH_2C(CH_3)_2CH_2-$	n-propyl
ethyl	methyl	$-CH_2C(CH_3)_2CH_2-$	n-butyl
ethyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
ethyl	methyl	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
n-propyl	hydrogen	$-(CH_2)-$	methyl
n-propyl	hydrogen	$-(CH_2)-$	ethyl
n-propyl	hydrogen	$-(CH_2)-$	n-propyl

n-propyl	hydrogen	-(CH_2)-	n-butyl
n-propyl	hydrogen	-(CH_2)-	ethoxymethyl
n-propyl	hydrogen	-(CH_2)-	2-methoxyethyl
n-propyl	hydrogen	-$(CH_2)_2$-	methyl
n-propyl	hydrogen	-$(CH_2)_2$-	ethyl
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n-propyl	hydrogen	-$(CH_2)_2$-	ethoxymethyl
n-propyl	hydrogen	-$(CH_2)_2$-	2-methoxyethyl
n-propyl	hydrogen	-$(CH_2)_3$-	methyl
n-propyl	hydrogen	-$(CH_2)_3$-	ethyl
n-propyl	hydrogen	-$(CH_2)_3$-	n-propyl
n-propyl	hydrogen	-$(CH_2)_3$-	n-butyl
n-propyl	hydrogen	-$(CH_2)_3$-	ethoxymethyl
n-propyl	hydrogen	-$(CH_2)_3$-	2-methoxyethyl
n-propyl	hydrogen	-$CH_2C(CH_3)_2$-	methyl
n-propyl	hydrogen	-$CH_2C(CH_3)_2$-	ethyl
n-propyl	hydrogen	-$CH_2C(CH_3)_2$-	n-propyl
n-propyl	hydrogen	-$CH_2C(CH_3)_2$-	n-butyl
n-propyl	hydrogen	-$CH_2C(CH_3)_2$-	ethoxymethyl
n-propyl	hydrogen	-$CH_2C(CH_3)_2$-	2-methoxyethyl
n-propyl	hydrogen	-$CH_2C(CH_3)_2CH_2$-	methyl
n-propyl	hydrogen	-$CH_2C(CH_3)_2CH_2$-	ethyl
n-propyl	hydrogen	-$CH_2C(CH_3)_2CH_2$-	n-propyl
n-propyl	hydrogen	-$CH_2C(CH_3)_2CH_2$-	n-butyl
n-propyl	hydrogen	-$CH_2C(CH_3)_2CH_2$-	ethoxymethyl
n-propyl	hydrogen	-$CH_2C(CH_3)_2CH_2$-	2-methoxyethyl
n-propyl	methyl	-(CH_2)-	methyl
n-propyl	methyl	-(CH_2)-	ethyl
n-propyl	methyl	-(CH_2)-	n-propyl
n-propyl	methyl	-(CH_2)-	n-butyl
n-propyl	methyl	-(CH_2)-	ethoxymethyl
n-propyl	methyl	-(CH_2)-	2-methoxyethyl
n-propyl	methyl	-$(CH_2)_2$-	methyl
n-propyl	methyl	-$(CH_2)_2$-	ethyl
n-propyl	methyl	-$(CH_2)_2$-	n-propyl
n-propyl	methyl	-$(CH_2)_2$-	n-butyl
n-propyl	methyl	-$(CH_2)_2$-	ethoxymethyl
n-propyl	methyl	-$(CH_2)_2$-	2-methoxyethyl
n-propyl	methyl	-$(CH_2)_3$-	methyl
n-propyl	methyl	-$(CH_2)_3$-	ethyl
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n-propyl	methyl	-$(CH_2)_3$-	ethoxymethyl
n-propyl	methyl	-$(CH_2)_3$-	2-methoxyethyl
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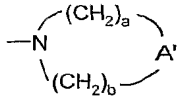
n-propyl	methyl	-$CH_2C(CH_3)_2$-	ethyl
n-propyl	methyl	-$CH_2C(CH_3)_2$-	n-propyl
n-propyl	methyl	-$CH_2C(CH_3)_2$-	n-butyl
n-propyl	methyl	-$CH_2C(CH_3)_2$-	ethoxymethyl

n-propyl	methyl	$-CH_2C(CH_3)_2-$	2-methoxyethyl
n-propyl	methyl	$-CH_2C(CH_3)_2CH_2-$	methyl
n-propyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethyl
n-propyl	methyl	$-CH_2C(CH_3)_2CH_2-$	n-propyl
n-propyl	methyl	$-CH_2C(CH_3)_2CH_2-$	n-butyl
n-propyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
n-propyl	methyl	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
n-butyl	hydrogen	$-(CH_2)-$	methyl
n-butyl	hydrogen	$-(CH_2)-$	ethyl
n-butyl	hydrogen	$-(CH_2)-$	n-propyl
n-butyl	hydrogen	$-(CH_2)-$	n-butyl
n-butyl	hydrogen	$-(CH_2)-$	ethoxymethyl
n-butyl	hydrogen	$-(CH_2)-$	2-methoxyethyl
n-butyl	hydrogen	$-(CH_2)_2-$	methyl
n-butyl	hydrogen	$-(CH_2)_2-$	ethyl
n-butyl	hydrogen	$-(CH_2)_2-$	n-propyl
n-butyl	hydrogen	$-(CH_2)_2-$	n-butyl
n-butyl	hydrogen	$-(CH_2)_2-$	ethoxymethyl
n-butyl	hydrogen	$-(CH_2)_2-$	2-methoxyethyl
n-butyl	hydrogen	$-(CH_2)_3-$	methyl
n-butyl	hydrogen	$-(CH_2)_3-$	ethyl
n-butyl	hydrogen	$-(CH_2)_3-$	n-propyl
n-butyl	hydrogen	$-(CH_2)_3-$	n-butyl
n-butyl	hydrogen	$-(CH_2)_3-$	ethoxymethyl
n-butyl	hydrogen	$-(CH_2)_3-$	2-methoxyethyl
n-butyl	hydrogen	$-CH_2C(CH_3)_2-$	methyl
n-butyl	hydrogen	$-CH_2C(CH_3)_2-$	ethyl
n-butyl	hydrogen	$-CH_2C(CH_3)_2-$	n-propyl
n-butyl	hydrogen	$-CH_2C(CH_3)_2-$	n-butyl
n-butyl	hydrogen	$-CH_2C(CH_3)_2-$	ethoxymethyl
n-butyl	hydrogen	$-CH_2C(CH_3)_2-$	2-methoxyethyl
n-butyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	methyl
n-butyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethyl
n-butyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	n-propyl
n-butyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	n-butyl
n-butyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
n-butyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
n-butyl	methyl	$-(CH_2)-$	methyl
n-butyl	methyl	$-(CH_2)-$	ethyl
n-butyl	methyl	$-(CH_2)-$	n-propyl
n-butyl	methyl	$-(CH_2)-$	n-butyl
n-butyl	methyl	$-(CH_2)-$	ethoxymethyl
n-butyl	methyl	$-(CH_2)-$	2-methoxyethyl
n-butyl	methyl	$-(CH_2)_2-$	methyl
n-butyl	methyl	$-(CH_2)_2-$	ethyl
n-butyl	methyl	$-(CH_2)_2-$	n-propyl
n-butyl	methyl	$-(CH_2)_2-$	n-butyl
n-butyl	methyl	$-(CH_2)_2-$	ethoxymethyl
n-butyl	methyl	$-(CH_2)_2-$	2-methoxyethyl
n-butyl	methyl	$-(CH_2)_3-$	methyl

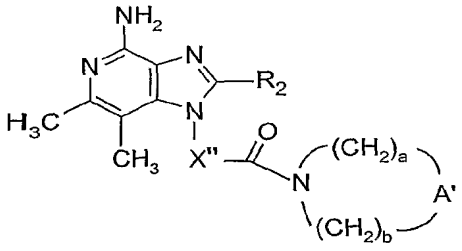
n-butyl	methyl	$-(CH_2)_3-$	ethyl
n-butyl	methyl	$-(CH_2)_3-$	n-propyl
n-butyl	methyl	$-(CH_2)_3-$	n-butyl
n-butyl	methyl	$-(CH_2)_3-$	ethoxymethyl
n-butyl	methyl	$-(CH_2)_3-$	2-methoxyethyl
n-butyl	methyl	$-CH_2C(CH_3)_2-$	methyl
n-butyl	methyl	$-CH_2C(CH_3)_2-$	ethyl
n-butyl	methyl	$-CH_2C(CH_3)_2-$	n-propyl
n-butyl	methyl	$-CH_2C(CH_3)_2-$	n-butyl
n-butyl	methyl	$-CH_2C(CH_3)_2-$	ethoxymethyl
n-butyl	methyl	$-CH_2C(CH_3)_2-$	2-methoxyethyl
n-butyl	methyl	$-CH_2C(CH_3)_2CH_2-$	methyl
n-butyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethyl
n-butyl	methyl	$-CH_2C(CH_3)_2CH_2-$	n-propyl
n-butyl	methyl	$-CH_2C(CH_3)_2CH_2-$	n-butyl
n-butyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
n-butyl	methyl	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
phenyl	hydrogen	$-(CH_2)-$	methyl
phenyl	hydrogen	$-(CH_2)-$	ethyl
phenyl	hydrogen	$-(CH_2)-$	n-propyl
phenyl	hydrogen	$-(CH_2)-$	n-butyl
phenyl	hydrogen	$-(CH_2)-$	ethoxymethyl
phenyl	hydrogen	$-(CH_2)-$	2-methoxyethyl
phenyl	hydrogen	$-(CH_2)_2-$	methyl
phenyl	hydrogen	$-(CH_2)_2-$	ethyl
phenyl	hydrogen	$-(CH_2)_2-$	n-propyl
phenyl	hydrogen	$-(CH_2)_2-$	n-butyl
phenyl	hydrogen	$-(CH_2)_2-$	ethoxymethyl
phenyl	hydrogen	$-(CH_2)_2-$	2-methoxyethyl
phenyl	hydrogen	$-(CH_2)_3-$	methyl
phenyl	hydrogen	$-(CH_2)_3-$	ethyl
phenyl	hydrogen	$-(CH_2)_3-$	n-propyl
phenyl	hydrogen	$-(CH_2)_3-$	n-butyl
phenyl	hydrogen	$-(CH_2)_3-$	ethoxymethyl
phenyl	hydrogen	$-(CH_2)_3-$	2-methoxyethyl
phenyl	hydrogen	$-CH_2C(CH_3)_2-$	methyl
phenyl	hydrogen	$-CH_2C(CH_3)_2-$	ethyl
phenyl	hydrogen	$-CH_2C(CH_3)_2-$	n-propyl
phenyl	hydrogen	$-CH_2C(CH_3)_2-$	n-butyl
phenyl	hydrogen	$-CH_2C(CH_3)_2-$	ethoxymethyl
phenyl	hydrogen	$-CH_2C(CH_3)_2-$	2-methoxyethyl
phenyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	methyl
phenyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethyl
phenyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	n-propyl
phenyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	n-butyl
phenyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
phenyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
phenyl	methyl	$-(CH_2)-$	methyl
phenyl	methyl	$-(CH_2)-$	ethyl
phenyl	methyl	$-(CH_2)-$	n-propyl

phenyl	methyl	-(CH_2)-	n-butyl
phenyl	methyl	-(CH_2)-	ethoxymethyl
phenyl	methyl	-(CH_2)-	2-methoxyethyl
phenyl	methyl	-$(CH_2)_2$-	methyl
phenyl	methyl	-$(CH_2)_2$-	ethyl
phenyl	methyl	-$(CH_2)_2$-	n-propyl
phenyl	methyl	-$(CH_2)_2$-	n-butyl
phenyl	methyl	-$(CH_2)_2$-	ethoxymethyl
phenyl	methyl	-$(CH_2)_2$-	2-methoxyethyl
phenyl	methyl	-$(CH_2)_3$-	methyl
phenyl	methyl	-$(CH_2)_3$-	ethyl
phenyl	methyl	-$(CH_2)_3$-	n-propyl
phenyl	methyl	-$(CH_2)_3$-	n-butyl
phenyl	methyl	-$(CH_2)_3$-	ethoxymethyl
phenyl	methyl	-$(CH_2)_3$-	2-methoxyethyl
phenyl	methyl	-$CH_2C(CH_3)_2$-	methyl
phenyl	methyl	-$CH_2C(CH_3)_2$-	ethyl
phenyl	methyl	-$CH_2C(CH_3)_2$-	n-propyl
phenyl	methyl	-$CH_2C(CH_3)_2$-	n-butyl
phenyl	methyl	-$CH_2C(CH_3)_2$-	ethoxymethyl
phenyl	methyl	-$CH_2C(CH_3)_2$-	2-methoxyethyl
phenyl	methyl	-$CH_2C(CH_3)_2CH_2$-	methyl
phenyl	methyl	-$CH_2C(CH_3)_2CH_2$-	ethyl
phenyl	methyl	-$CH_2C(CH_3)_2CH_2$-	n-propyl
phenyl	methyl	-$CH_2C(CH_3)_2CH_2$-	n-butyl
phenyl	methyl	-$CH_2C(CH_3)_2CH_2$-	ethoxymethyl
phenyl	methyl	-$CH_2C(CH_3)_2CH_2$-	2-methoxyethyl

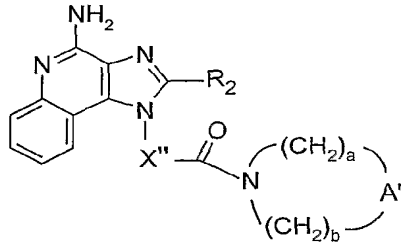
Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas (IIIb, IVe, Vd, or VIc) and the following



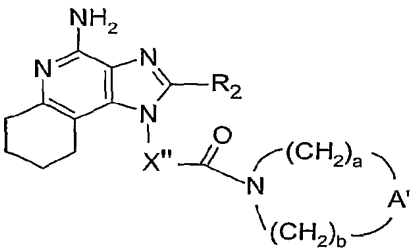
, X", and R_2 substituents, wherein each line of the table is matched with Formula IIIb, IVe, Vd, or VIc to represent a specific embodiment of the invention.



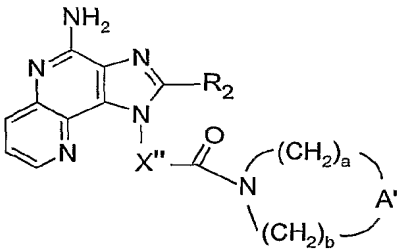
IIIb



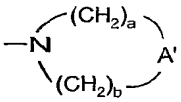
IVe



Vd



VIc

	X"	R_2
pyrrolidin-1-yl	-(CH_2)-	methyl
pyrrolidin-1-yl	-(CH_2)-	ethyl
pyrrolidin-1-yl	-(CH_2)-	n-propyl
pyrrolidin-1-yl	-(CH_2)-	n-butyl
pyrrolidin-1-yl	-(CH_2)-	ethoxymethyl
pyrrolidin-1-yl	-(CH_2)-	2-methoxyethyl
pyrrolidin-1-yl	-$(CH_2)_2$-	methyl
pyrrolidin-1-yl	-$(CH_2)_2$-	ethyl
pyrrolidin-1-yl	-$(CH_2)_2$-	n-propyl
pyrrolidin-1-yl	-$(CH_2)_2$-	n-butyl
pyrrolidin-1-yl	-$(CH_2)_2$-	ethoxymethyl
pyrrolidin-1-yl	-$(CH_2)_2$-	2-methoxyethyl
pyrrolidin-1-yl	-$(CH_2)_3$-	methyl
pyrrolidin-1-yl	-$(CH_2)_3$-	ethyl
pyrrolidin-1-yl	-$(CH_2)_3$-	n-propyl
pyrrolidin-1-yl	-$(CH_2)_3$-	n-butyl
pyrrolidin-1-yl	-$(CH_2)_3$-	ethoxymethyl
pyrrolidin-1-yl	-$(CH_2)_3$-	2-methoxyethyl
pyrrolidin-1-yl	-$CH_2C(CH_3)_2$-	methyl
pyrrolidin-1-yl	-$CH_2C(CH_3)_2$-	ethyl
pyrrolidin-1-yl	-$CH_2C(CH_3)_2$-	n-propyl
pyrrolidin-1-yl	-$CH_2C(CH_3)_2$-	n-butyl
pyrrolidin-1-yl	-$CH_2C(CH_3)_2$-	ethoxymethyl
pyrrolidin-1-yl	-$CH_2C(CH_3)_2$-	2-methoxyethyl
pyrrolidin-1-yl	-$CH_2C(CH_3)_2CH_2$-	methyl
pyrrolidin-1-yl	-$CH_2C(CH_3)_2CH_2$-	ethyl
pyrrolidin-1-yl	-$CH_2C(CH_3)_2CH_2$-	n-propyl
pyrrolidin-1-yl	-$CH_2C(CH_3)_2CH_2$-	n-butyl
pyrrolidin-1-yl	-$CH_2C(CH_3)_2CH_2$-	ethoxymethyl
pyrrolidin-1-yl	-$CH_2C(CH_3)_2CH_2$-	2-methoxyethyl
piperidin-1-yl	-(CH_2)-	methyl
piperidin-1-yl	-(CH_2)-	ethyl
piperidin-1-yl	-(CH_2)-	n-propyl
piperidin-1-yl	-(CH_2)-	n-butyl
piperidin-1-yl	-(CH_2)-	ethoxymethyl

piperidin-1-yl	$-(CH_2)-$	2-methoxyethyl
piperidin-1-yl	$-(CH_2)_2-$	methyl
piperidin-1-yl	$-(CH_2)_2-$	ethyl
piperidin-1-yl	$-(CH_2)_2-$	n-propyl
piperidin-1-yl	$-(CH_2)_2-$	n-butyl
piperidin-1-yl	$-(CH_2)_2-$	ethoxymethyl
piperidin-1-yl	$-(CH_2)_2-$	2-methoxyethyl
piperidin-1-yl	$-(CH_2)_3-$	methyl
piperidin-1-yl	$-(CH_2)_3-$	ethyl
piperidin-1-yl	$-(CH_2)_3-$	n-propyl
piperidin-1-yl	$-(CH_2)_3-$	n-butyl
piperidin-1-yl	$-(CH_2)_3-$	ethoxymethyl
piperidin-1-yl	$-(CH_2)_3-$	2-methoxyethyl
piperidin-1-yl	$-CH_2C(CH_3)_2-$	methyl
piperidin-1-yl	$-CH_2C(CH_3)_2-$	ethyl
piperidin-1-yl	$-CH_2C(CH_3)_2-$	n-propyl
piperidin-1-yl	$-CH_2C(CH_3)_2-$	n-butyl
piperidin-1-yl	$-CH_2C(CH_3)_2-$	ethoxymethyl
piperidin-1-yl	$-CH_2C(CH_3)_2-$	2-methoxyethyl
piperidin-1-yl	$-CH_2C(CH_3)_2CH_2-$	methyl
piperidin-1-yl	$-CH_2C(CH_3)_2CH_2-$	ethyl
piperidin-1-yl	$-CH_2C(CH_3)_2CH_2-$	n-propyl
piperidin-1-yl	$-CH_2C(CH_3)_2CH_2-$	n-butyl
piperidin-1-yl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
piperidin-1-yl	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
4-acetylpiperazin-1-yl	$-(CH_2)-$	methyl
4-acetylpiperazin-1-yl	$-(CH_2)-$	ethyl
4-acetylpiperazin-1-yl	$-(CH_2)-$	n-propyl
4-acetylpiperazin-1-yl	$-(CH_2)-$	n-butyl
4-acetylpiperazin-1-yl	$-(CH_2)-$	ethoxymethyl
4-acetylpiperazin-1-yl	$-(CH_2)-$	2-methoxyethyl
4-acetylpiperazin-1-yl	$-(CH_2)_2-$	methyl
4-acetylpiperazin-1-yl	$-(CH_2)_2-$	ethyl
4-acetylpiperazin-1-yl	$-(CH_2)_2-$	n-propyl
4-acetylpiperazin-1-yl	$-(CH_2)_2-$	n-butyl
4-acetylpiperazin-1-yl	$-(CH_2)_2-$	ethoxymethyl
4-acetylpiperazin-1-yl	$-(CH_2)_2-$	2-methoxyethyl
4-acetylpiperazin-1-yl	$-(CH_2)_3-$	methyl
4-acetylpiperazin-1-yl	$-(CH_2)_3-$	ethyl
4-acetylpiperazin-1-yl	$-(CH_2)_3-$	n-propyl
4-acetylpiperazin-1-yl	$-(CH_2)_3-$	n-butyl
4-acetylpiperazin-1-yl	$-(CH_2)_3-$	ethoxymethyl
4-acetylpiperazin-1-yl	$-(CH_2)_3-$	2-methoxyethyl
4-acetylpiperazin-1-yl	$-CH_2C(CH_3)_2-$	methyl
4-acetylpiperazin-1-yl	$-CH_2C(CH_3)_2-$	ethyl
4-acetylpiperazin-1-yl	$-CH_2C(CH_3)_2-$	n-propyl
4-acetylpiperazin-1-yl	$-CH_2C(CH_3)_2-$	n-butyl
4-acetylpiperazin-1-yl	$-CH_2C(CH_3)_2-$	ethoxymethyl
4-acetylpiperazin-1-yl	$-CH_2C(CH_3)_2-$	2-methoxyethyl
4-acetylpiperazin-1-yl	$-CH_2C(CH_3)_2CH_2-$	methyl

4-acetylpiperazin-1-yl	$-CH_2C(CH_3)_2CH_2-$	ethyl
4-acetylpiperazin-1-yl	$-CH_2C(CH_3)_2CH_2-$	n-propyl
4-acetylpiperazin-1-yl	$-CH_2C(CH_3)_2CH_2-$	n-butyl
4-acetylpiperazin-1-yl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
4-acetylpiperazin-1-yl	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
morpholin-4-yl	$-(CH_2)-$	methyl
morpholin-4-yl	$-(CH_2)-$	ethyl
morpholin-4-yl	$-(CH_2)-$	n-propyl
morpholin-4-yl	$-(CH_2)-$	n-butyl
morpholin-4-yl	$-(CH_2)-$	ethoxymethyl
morpholin-4-yl	$-(CH_2)-$	2-methoxyethyl
morpholin-4-yl	$-(CH_2)_2-$	methyl
morpholin-4-yl	$-(CH_2)_2-$	ethyl
morpholin-4-yl	$-(CH_2)_2-$	n-propyl
morpholin-4-yl	$-(CH_2)_2-$	n-butyl
morpholin-4-yl	$-(CH_2)_2-$	ethoxymethyl
morpholin-4-yl	$-(CH_2)_2-$	2-methoxyethyl
morpholin-4-yl	$-(CH_2)_3-$	methyl
morpholin-4-yl	$-(CH_2)_3-$	ethyl
morpholin-4-yl	$-(CH_2)_3-$	n-propyl
morpholin-4-yl	$-(CH_2)_3-$	n-butyl
morpholin-4-yl	$-(CH_2)_3-$	ethoxymethyl
morpholin-4-yl	$-(CH_2)_3-$	2-methoxyethyl
morpholin-4-yl	$-CH_2C(CH_3)_2-$	methyl
morpholin-4-yl	$-CH_2C(CH_3)_2-$	ethyl
morpholin-4-yl	$-CH_2C(CH_3)_2-$	n-propyl
morpholin-4-yl	$-CH_2C(CH_3)_2-$	n-butyl
morpholin-4-yl	$-CH_2C(CH_3)_2-$	ethoxymethyl
morpholin-4-yl	$-CH_2C(CH_3)_2-$	2-methoxyethyl
morpholin-4-yl	$-CH_2C(CH_3)_2CH_2-$	methyl
morpholin-4-yl	$-CH_2C(CH_3)_2CH_2-$	ethyl
morpholin-4-yl	$-CH_2C(CH_3)_2CH_2-$	n-propyl
morpholin-4-yl	$-CH_2C(CH_3)_2CH_2-$	n-butyl
morpholin-4-yl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
morpholin-4-yl	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)-$	methyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)-$	ethyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)-$	n-propyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)-$	n-butyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)-$	ethoxymethyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)-$	2-methoxyethyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)_2-$	methyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)_2-$	ethyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)_2-$	n-propyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)_2-$	n-butyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)_2-$	ethoxymethyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)_2-$	2-methoxyethyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)_3-$	methyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)_3-$	ethyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)_3-$	n-propyl

1,1-dioxothiomorpholin-4-yl	$-(CH_2)_3-$	n-butyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)_3-$	ethoxymethyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)_3-$	2-methoxyethyl
1,1-dioxothiomorpholin-4-yl	$-CH_2C(CH_3)_2-$	methyl
1,1-dioxothiomorpholin-4-yl	$-CH_2C(CH_3)_2-$	ethyl
1,1-dioxothiomorpholin-4-yl	$-CH_2C(CH_3)_2-$	n-propyl
1,1-dioxothiomorpholin-4-yl	$-CH_2C(CH_3)_2-$	n-butyl
1,1-dioxothiomorpholin-4-yl	$-CH_2C(CH_3)_2-$	ethoxymethyl
1,1-dioxothiomorpholin-4-yl	$-CH_2C(CH_3)_2-$	2-methoxyethyl
1,1-dioxothiomorpholin-4-yl	$-CH_2C(CH_3)_2CH_2-$	methyl
1,1-dioxothiomorpholin-4-yl	$-CH_2C(CH_3)_2CH_2-$	ethyl
1,1-dioxothiomorpholin-4-yl	$-CH_2C(CH_3)_2CH_2-$	n-propyl
1,1-dioxothiomorpholin-4-yl	$-CH_2C(CH_3)_2CH_2-$	n-butyl
1,1-dioxothiomorpholin-4-yl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
1,1-dioxothiomorpholin-4-yl	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl

CYTOKINE INDUCTION IN HUMAN CELLS

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon (α) and tumor necrosis factor (α) (IFN-α and TNF-α, respectively) secreted into culture media as described by Testerman et. al. in "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", *Journal of Leukocyte Biology, 58*, 365-372 (September, 1995).

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into vacutainer tubes or syringes containing EDTA. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077 (Sigma, St. Louis, MO) or Ficoll-Paque Plus (Amersham Biosciences Piscataway, NJ). Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). Alternately, whole blood is placed in Accuspin (Sigma) or LeucoSep (Greiner Bio-One, Inc., Longwood, FL) centrifuge frit tubes containing density gradient medium. The PBMC layer is collected and washed twice with DPBS or HBSS and re-suspended at 4×10^6 cells/mL in RPMI complete. The PBMC suspension is added to 96 well flat bottom sterile tissue culture plates containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 μM. Controls include cell samples with media only, cell samples with DMSO only (no compound), and cell samples with reference compound.

Incubation

The solution of test compound is added at 60 μM to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range (usually 30-0.014 μM). The final concentration of PBMC suspension is 2 x 10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 x g) at 4°C. The cell-free culture supernatant is removed and transferred to sterile polypropylene tubes. Samples are maintained at -30 to -70°C until analysis. The samples are analyzed for IFN-α by ELISA and for TNF-α by IGEN/BioVeris Assay.

Interferon (α) and Tumor Necrosis Factor (α) Analysis

IFN-α concentration is determined with a human multi-subtype colorimetric sandwich ELISA (Catalog Number 41105) from PBL Biomedical Laboratories, Piscataway, NJ. Results are expressed in pg/mL.

The TNF-α concentration is determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from BioVeris Corporation, formerly known as IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF-α capture and detection antibody pair (Catalog Numbers AHC3419 and AHC3712) from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

Assay Data and Analysis

In total, the data output of the assay consists of concentration values of TNF-α and IFN-α (y-axis) as a function of compound concentration (x-axis).

Analysis of the data has two steps. First, the greater of the mean DMSO (DMSO control wells) or the experimental background (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α) is subtracted from each reading. If any negative values result from background subtraction, the reading is reported as " * ", and is noted as not reliably detectable. In subsequent calculations and statistics, " * ", is treated as a zero. Second, all background subtracted values are multiplied by a single adjustment ratio to decrease experiment to experiment variability. The adjustment ratio is the area of the reference compound in the new experiment divided by the expected area of the reference compound based on the past 61 experiments (unadjusted readings). This results in the scaling of the reading (y-axis) for the new data without changing the shape of the dose-response curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) and the expected area is the sum of the median dose values from the past 61 experiments.

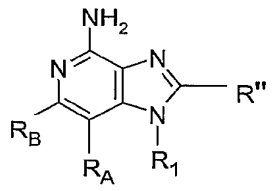
The minimum effective concentration is calculated based on the background-subtracted, reference-adjusted results for a given experiment and compound. The minimum effective concentration (μmolar) is the lowest of the tested compound concentrations that induces a response over a fixed cytokine concentration for the tested cytokine (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α). The maximal response (pg/mL) is the maximal response attained in the dose response curve.

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and

embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

WHAT IS CLAIMED IS:

1. A compound of the formula (I):

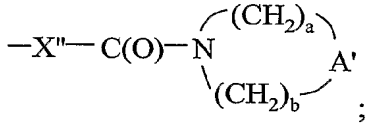


I

wherein:

R_1 is selected from the group consisting of:

-X'-C(O)-N(R_1')(R_1") and



;

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-;

X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
amino,
alkylamino,
dialkylamino,
arylsulfonyl, and
alkylsulfonyl;

A' is selected from the group consisting of -O-, –C(O)-, -CH_2-, -$S(O)_{0-2}$-, and -N(Q-R_4)-;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_A and R_B are independently selected from the group consisting of:

hydrogen,
halogen,
alkyl,
alkenyl,
alkoxy,
alkylthio, and
-$N(R_9)_2$;

or R_A and R_B taken together form either a fused aryl ring that is unsubstituted or substituted by one or more R_a groups, or a fused 5 to 7 membered saturated ring that is unsubstituted or substituted by one or more R_c groups;

or R_A and R_B taken together form a fused heteroaryl or 5 to 7 membered saturated ring containing one heteroatom selected from the group consisting of N and S, wherein the heteroaryl ring is unsubstituted or substituted by one or more R_b groups, and the 5 to 7 membered saturated ring is unsubstituted or substituted by one or more R_c groups;

R_a is selected from the group consisting of:

halogen,

alkyl,

haloalkyl,

alkoxy, and

$-N(R_9)_2$;

R_b is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

haloalkyl,

alkoxy, and

$-N(R_9)_2$;

R_c is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

W is selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkyl arylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro,

hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_6 is selected from the group consisting of =O and =S;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

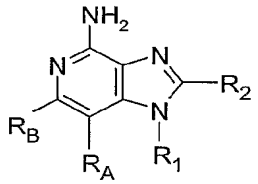
R_9 is selected from the group consisting of hydrogen and alkyl; and

R" is hydrogen or a non-interfering substituent;

with the proviso that when R_A and R_B form a fused heteroaryl or 5 to 7 membered saturated ring containing one heteroatom selected from the group consisting of N and S, wherein the heteroaryl ring is unsubstituted or substituted by one or more R_b groups, and the 5 to 7 membered saturated ring is unsubstituted or substituted by one or more R_c groups, then R_1 can also be -X"-C(O)-N(R_1')(R_1");

or a pharmaceutically acceptable salt thereof.

2. A compound of the formula (II):

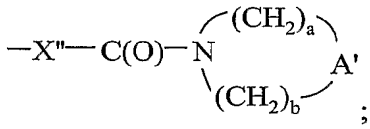


II

wherein:

R_1 is selected from the group consisting of:

-X'-C(O)-N(R_1')(R_1") and



;

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-;

X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and

-CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,

halogen,

cyano,

nitro,

amino,

alkylamino,

dialkylamino,

arylsulfonyl, and

alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, -CH_2-, -$S(O)_{0-2}$-, and -N(Q-R_4)-;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_A and R_B are independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

or R_A and R_B taken together form either a fused aryl ring that is unsubstituted or substituted by one or more R_a groups, or a fused 5 to 7 membered saturated ring that is unsubstituted or substituted by one or more R_c groups;

or R_A and R_B taken together form a fused heteroaryl or 5 to 7 membered saturated ring containing one heteroatom selected from the group consisting of N and S, wherein the heteroaryl ring is unsubstituted or substituted by one or more R_b groups, and the 5 to 7 membered saturated ring is unsubstituted or substituted by one or more R_c groups;

R_a is selected from the group consisting of:

halogen,

alkyl,

haloalkyl,

alkoxy, and

$-N(R_9)_2$;

R_b is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

haloalkyl,

alkoxy, and

$-N(R_9)_2$;

R_c is selected from the group consisting of:

halogen,

hydroxy,

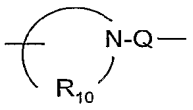
alkyl,

alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

R_2 is selected from the group consisting of:
$-R_4$,
$-X-R_4$,
$-X-Y-R_4$, and
$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:
$-S(O)_{0-2}-$,
$-S(O)_2-N(R_8)-$,
$-C(R_6)-$,
$-C(R_6)-O-$,
$-O-C(R_6)-$,
$-O-C(O)-O-$,
$-N(R_8)-Q-$,
$-C(R_6)-N(R_8)-$,
$-O-C(R_6)-N(R_8)-$,
$-C(R_6)-N(OR_9)-$,



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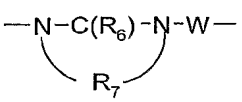

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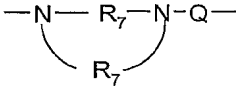

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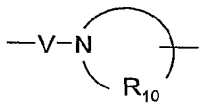
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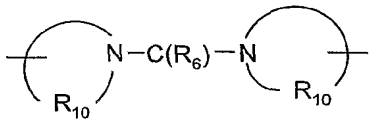
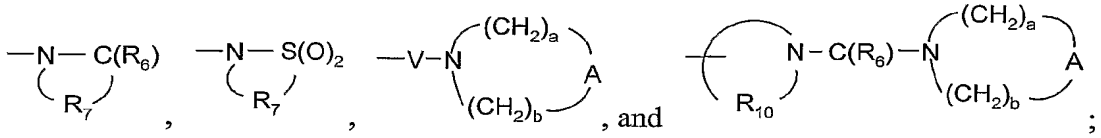

;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and

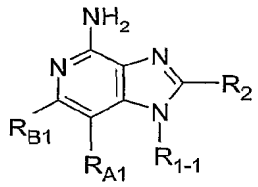
-$S(O)_2$-; and

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2$-;

with the proviso that when R_A and R_B form a fused heteroaryl or 5 to 7 membered saturated ring containing one heteroatom selected from the group consisting of N and S, wherein the heteroaryl ring is unsubstituted or substituted by one or more R_b groups, and the 5 to 7 membered saturated ring is unsubstituted or substituted by one or more R_c groups, then R_1 can also be -X"-C(O)-N(R_1')(R_1");

or a pharmaceutically acceptable salt thereof.

3. A compound of the formula (III):

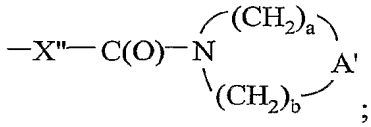


III

wherein:

R_{1-1} is selected from the group consisting of:

-X'-C(O)-N(R_1')(R_1") and



;

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-;

X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:
hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
amino,
alkylamino,
dialkylamino,
arylsulfonyl, and
alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_{A1} and R_{B1} are independently selected from the group consisting of:
hydrogen,
halogen,
alkyl,
alkenyl,
alkoxy,
alkylthio, and

$-N(R_9)_2$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

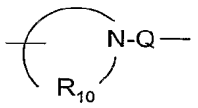
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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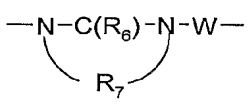

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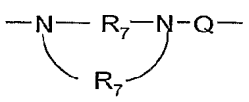

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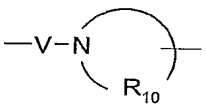
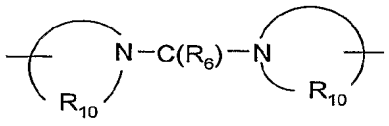


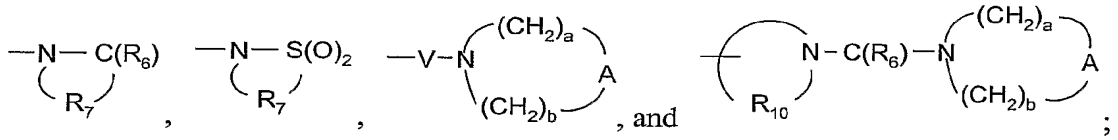
, and



;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

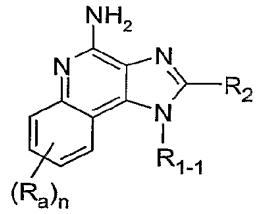
Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

4. A compound of the formula (IV):

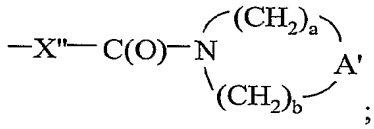


IV

wherein:

R_{1-1} is selected from the group consisting of:

$-X'-C(O)-N(R_1')(R_1'')$ and



;

X' is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene-, and $-CH(R_9)$-alkenylene-;

X" is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene-, and $-CH(R_9)$-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1'' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
amino,
alkylamino,
dialkylamino,
arylsulfonyl, and
alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_a is selected from the group consisting of:

halogen,
alkyl,
haloalkyl,
alkoxy, and
$-N(R_9)_2$;

n is an integer from 0 to 4;

R_2 is selected from the group consisting of:

$-R_4$,
$-X-R_4$,
$-X-Y-R_4$, and
$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

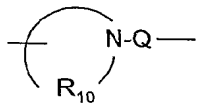
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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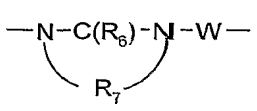

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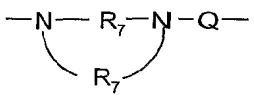

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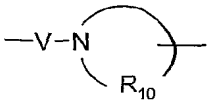
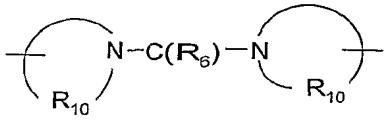


, and

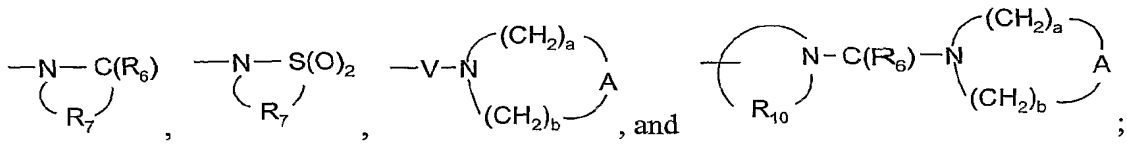


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy,

heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

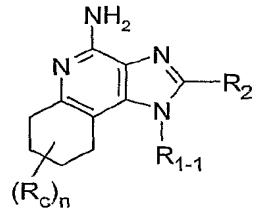
Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

5. A compound of the formula (V):

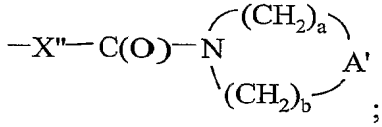


V

wherein:

R_{1-1} is selected from the group consisting of:

$-X'-C(O)-N(R_1')(R_1'')$ and



;

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-;

X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,

halogen,

cyano,

nitro,

amino,

alkylamino,

dialkylamino,
arylsulfonyl, and
alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, -CH_2-, -$S(O)_{0-2}$-, and -N(Q-R_4)-;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_c is selected from the group consisting of:

halogen,
hydroxy,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
-$N(R_9)_2$;

n is an integer from 0 to 4;

R_2 is selected from the group consisting of:

-R_4,
-X-R_4,
-X-Y-R_4, and
-X-R_5;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

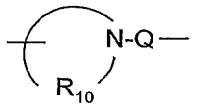
-$S(O)_{0-2}$-,
-$S(O)_2$-$N(R_8)$-,
-$C(R_6)$-,
-$C(R_6)$-O-,
-O-$C(R_6)$-,
-O-C(O)-O-,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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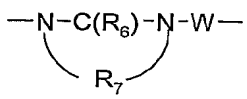

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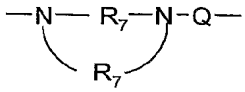

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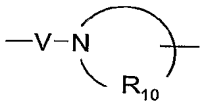

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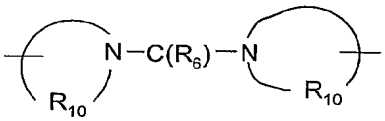
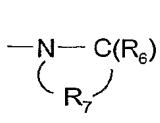


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



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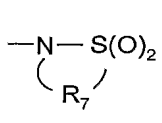

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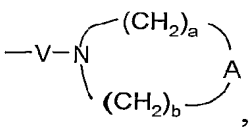
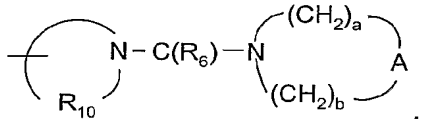


, and



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, -$S(O)_{0-2}$-, -CH_2-, and -$N(R_4)$-;

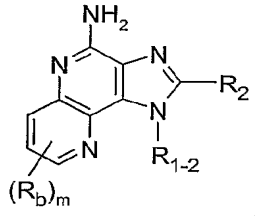
Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, and -$C(R_6)$-$N(OR_9)$-;

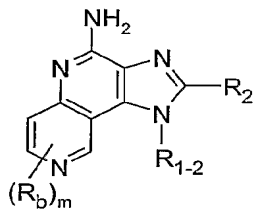
V is selected from the group consisting of -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-; and

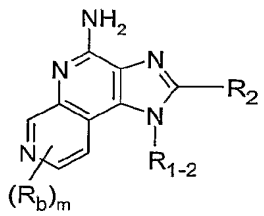
W is selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-;

or a pharmaceutically acceptable salt thereof.

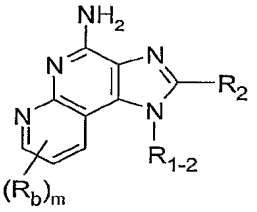
6. A compound selected from the group consisting of the formulas (VI, VII, VIII, and IX):


VI


VII


VIII

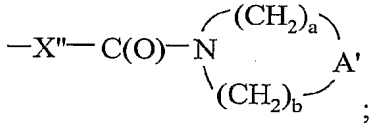
, and


IX

wherein:

R_{1-2} is selected from the group consisting of:

-X"-C(O)-$N(R_1')(R_1")$ and



;

X" is selected from the group consisting of -$CH(R_9)$-, -$CH(R_9)$-alkylene-, and -$CH(R_9)$-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,

halogen,

cyano,

nitro,

amino,

alkylamino,

dialkylamino,

arylsulfonyl, and

alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_b is selected from the group consisting of:

halogen,

hydroxy,
alkyl,
haloalkyl,
alkoxy, and
$-N(R_9)_2$;

m is an integer from 0 to 3;

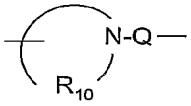
R_2 is selected from the group consisting of:

$-R_4$,
$-X-R_4$,
$-X-Y-R_4$, and
$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,
$-S(O)_2-N(R_8)-$,
$-C(R_6)-$,
$-C(R_6)-O-$,
$-O-C(R_6)-$,
$-O-C(O)-O-$,
$-N(R_8)-Q-$,
$-C(R_6)-N(R_8)-$,
$-O-C(R_6)-N(R_8)-$,
$-C(R_6)-N(OR_9)-$,



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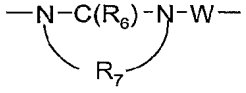

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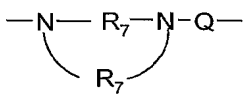
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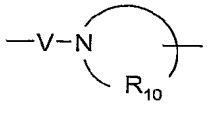
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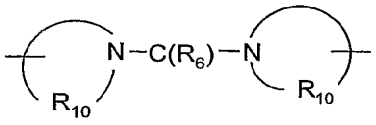
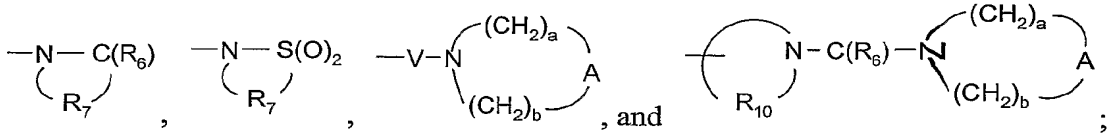

;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, -$S(O)_{0-2}$-, -CH_2-, and -$N(R_4)$-;

Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, and -C(R_6)-N(OR_9)-;

V is selected from the group consisting of -C(R_6)-, -O-C(R_6)-, -N(R_8)-C(R_6)-, and -S(O)$_2$-; and

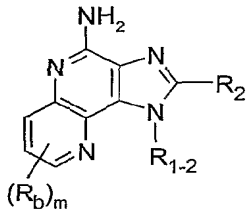
W is selected from the group consisting of a bond, -C(O)-, and -S(O)$_2$-;

or a pharmaceutically acceptable salt thereof.

7. The compound or salt of claim 1 or claim 2 wherein the fused aryl ring, fused heteroaryl ring, fused 5 to 7 membered saturated ring, or fused 5 to 7 membered saturated ring containing one N or S atom is unsubstituted.

8. The compound or salt of claim 3 wherein R_{A1} and R_{B1} are methyl.

9. The compound or salt of claim 6 wherein the compound is of the following formula (VI):

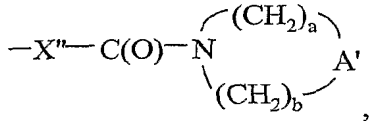


VI,

or a pharmaceutically acceptable salt thereof.

10. The compound or salt of claim 6 or claim 9 wherein m is 0.

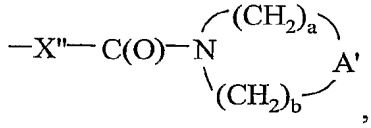
11. The compound or salt of any one of claims 6, 9, or 10 wherein R_{1-2} is



, A' is -O-, and a and b are each 2.

12. The compound or salt of claim 4 or claim 5 wherein n is 0.

13. The compound or salt of any one of claims 3, 4, 5, 8, and 12 wherein R_{1-1} is

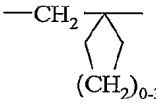

, A' is -O-, and a and b are each 2.

14. The compound or salt of any one of claims 1 through 5, 7, 8, and 12 wherein X' is $-CH_2-C_{0-10}$ alkylene- or X" is $-CH_2-C_{0-10}$ alkylene- or $-CH_2-C_{1-4}$ alkylene-O-C_{1-4} alkylene-.

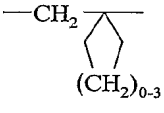
15. The compound or salt of claim 14 wherein X' is $-CH_2-C_{0-4}$ alkylene- or X" is $-CH_2-C_{0-4}$ alkylene- or $-CH_2-C_{1-4}$ alkylene-O-C_{1-4} alkylene-.

16. The compound or salt of claim 15 wherein X' is $-(CH_2)_{1-5}-$, $-CH_2C(CH_3)_2-$, or $-CH_2C(CH_3)_2CH_2-$; or X" is $-(CH_2)_{1-5}-$, $-CH_2C(CH_3)_2-$, $-CH_2C(CH_3)_2CH_2-$, or $-(CH_2)_3-O-CH_2-$.

17. The compound or salt of any one of claims 1 through 5, 7, 8, 12, and 14 wherein X' or X" is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2C(CH_3)_2-$, $-CH_2C(CH_3)_2CH_2-$, or


.

18. The compound or salt of claim 17 wherein X' or X" is $-CH_2-$, $-CH_2CH_2-$, $-CH_2C(CH_3)_2-$, or


.

19. The compound or salt of claim 16 or claim 18 wherein X' or X" is $-CH_2CH_2-$ or $-CH_2C(CH_3)_2-$.

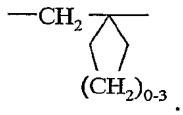
20. The compound or salt of any one of claims 1 through 14 wherein X" is $-CH_2-C_{0-10}$ alkylene- or $-CH_2-C_{1-4}$ alkylene-O-C_{1-4} alkylene-.

21. The compound or salt of claim 20 wherein X" is $-CH_2-C_{0-4}$ alkylene- or

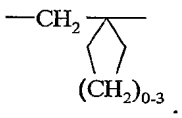
-CH_2-C_{1-4} alkylene-O-C_{1-4} alkylene-.

22. The compound or salt of claim 21 wherein X" is -$(CH_2)_{1-5}$-, -$CH_2C(CH_3)_2$-, -$CH_2C(CH_3)_2CH_2$-, or -$(CH_2)_3$-O-CH_2-.

23. The compound or salt of any one of claims 1 through 14, 17, and 20 wherein X" is -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-,-$CH_2C(CH_3)_2$-, -$CH_2C(CH_3)_2CH_2$-, or



24. The compound or salt of claim 23 wherein X" is -CH_2-, -CH_2CH_2-, -$CH_2C(CH_3)_2$-, or



25. The compound or salt of claim 22 or claim 24 wherein X" is -CH_2CH_2- or -$CH_2C(CH_3)_2$-.

26. The compound or salt of any one of claims 1 through 10, 12, 14 through 19; claims 20 through 22 as dependent on any one of claims 1 through 10, 12, and 14; and claims 23 through 25 as dependent on any one of claims 1 through 10, 12, 14, and 17 wherein R_1" is hydrogen.

27. The compound or salt of claim 26 wherein R_1' is hydrogen or C_{1-3} alkyl.

28. The compound or salt of claim 27 wherein R_1' and R_1" are hydrogen.

29. The compound or salt of any one of claims 1 through 10, 12, 14 through 19; claims 20 through 22 as dependent on any one of claims 1 through 10, 12, and 14; and claims 23 through 25 as dependent on any one of claims 1 through 10, 12, 14, and 17 wherein A' is -SO_2-, -O-, or -N(Q-R_4)-, and a and b are independently integers from 2 to 3; or A' is

-CH_2-, and a and b are independently integers from 1 to 3.

30. The compound or salt of any one of claims 2 through 6, 8 through 13, and claims 7 and 14 through 29 except as they are dependent on claim 1, wherein R_2 is hydrogen, alkoxyalkylenyl, hydroxyalkylenyl, -R_4, -X-R_4, or -X-Y-R_4; X is C_{1-2} alkylene; Y is -$S(O)_{0-2}$-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-, -$C(R_6)$-O-, -O-$C(R_6)$-, -O-C(O)-O-, -$N(R_8)$-Q-, -$C(R_6)$-$N(R_8)$-, -O-$C(R_6)$-$N(R_8)$-, or -$C(R_6)$-$N(OR_9)$-; and R_4 is alkyl.

31. The compound or salt of claim 30 wherein R_2 is hydrogen, C_{1-4} alkyl, hydroxyC_{1-4} alkylenyl, or C_{1-4} alkyl-O-C_{1-4} alkylenyl.

32. The compound or salt of claim 31 wherein R_2 is hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, ethoxymethyl, hydroxymethyl, or 2-hydroxyethyl.

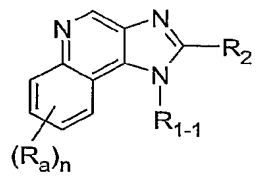
33. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of any one of claims 1 through 32 and a pharmaceutically acceptable carrier.

34. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of any one of claims 1 through 32 or a pharmaceutical composition of claim 33 to the animal.

35. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of claims 1 through 32 or a pharmaceutical composition of claim 33 to the animal.

36. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of claims 1 through 32 or a pharmaceutical composition of claim 33 to the animal.

37. A compound of the formula (XIV):

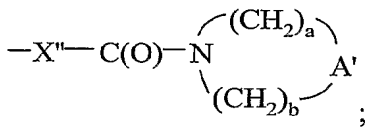


XIV

wherein:

R_{1-1} is selected from the group consisting of:

-X'-C(O)-N(R_1')(R_1") and



;

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-;

X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,
hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
amino,
alkylamino,
dialkylamino,
arylsulfonyl, and
alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$;

R_a is selected from the group consisting of:

halogen,
alkyl,
haloalkyl,
alkoxy, and
$-N(R_9)_2$;

n is an integer from 0 to 4;

R_2 is selected from the group consisting of:

$-R_4$,
$-X-R_4$,
$-X-Y-R_4$, and
$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

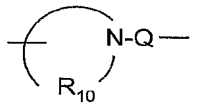
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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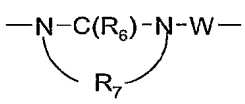

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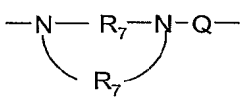

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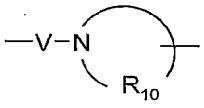
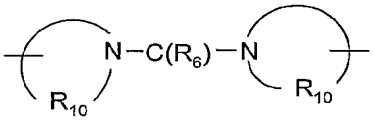


, and

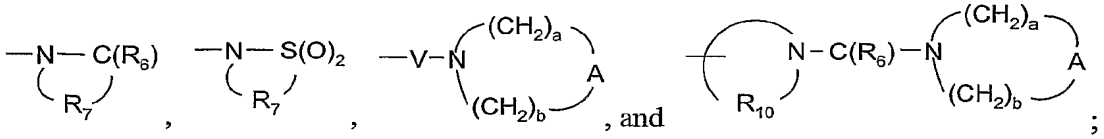


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino,

(dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

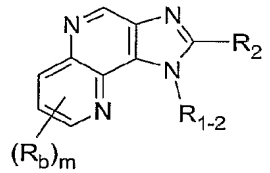
Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

38. A compound of the formula (XV):

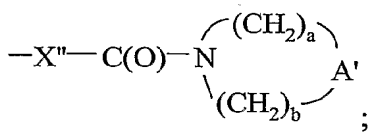


XV

wherein:

R_{1-2} is selected from the group consisting of:

$-X''-C(O)-N(R_1')(R_1'')$ and



;

X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,

halogen,

cyano,

nitro,

amino,

alkylamino,

dialkylamino,

arylsulfonyl, and

alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_b is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

haloalkyl,

alkoxy, and

$-N(R_9)_2$;

m is an integer from 0 to 3;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

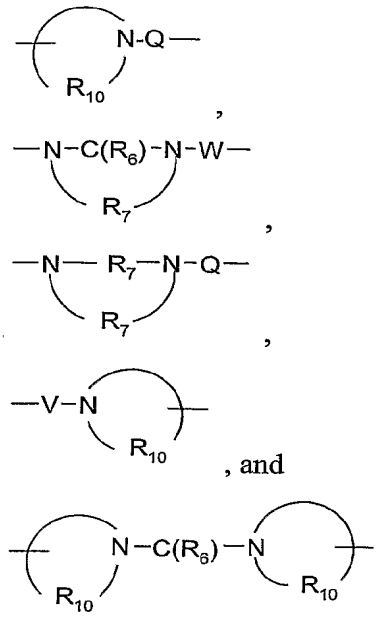
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,

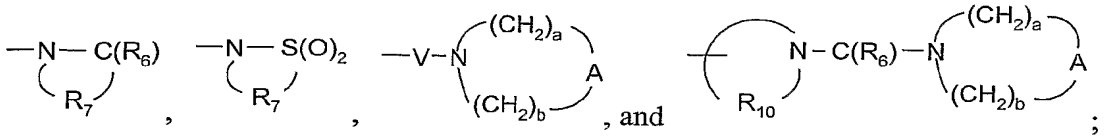


, and

;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



, and ;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, -$S(O)_{0-2}$-, -CH_2-, and -$N(R_4)$-;

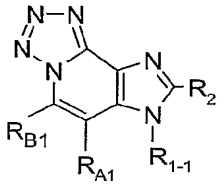
Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, and -$C(R_6)$-$N(OR_9)$-;

V is selected from the group consisting of -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-; and

W is selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-;

or a pharmaceutically acceptable salt thereof.

39. A compound of the formula (XVI):

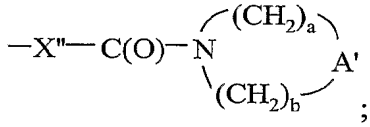


XVI

wherein:

R_{1-1} is selected from the group consisting of:

-X'-C(O)-$N(R_1')(R_1'')$ and



;

X' is selected from the group consisting of -$CH(R_9)$-, -$CH(R_9)$-alkylene-, and -$CH(R_9)$-alkenylene-;

X'' is selected from the group consisting of -$CH(R_9)$-, -$CH(R_9)$-alkylene-, and -$CH(R_9)$-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1'' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,
aryl,
arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:
hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
amino,
alkylamino,
dialkylamino,
arylsulfonyl, and
alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$;

R_{A1} and R_{B1} are independently selected from the group consisting of:
hydrogen,
halogen,
alkyl,
alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

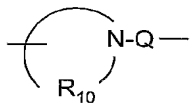
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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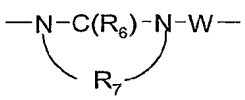

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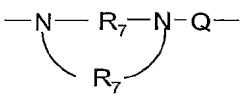

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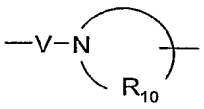
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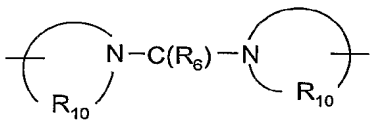
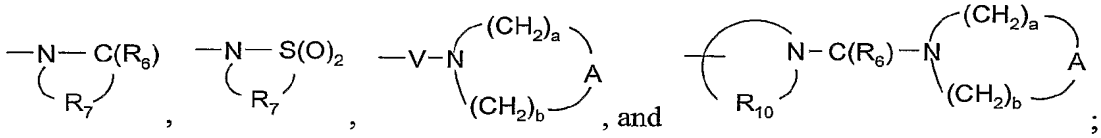

;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and

$-S(O)_2-$; and

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

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